Derivation of Proposed Groundwater

Interim Maximum Allowable Concentration (IMAC)

Bentazon

1. Introduction

North Carolina regulations [15A NCAC 02L.0202 (c)] allow a party to petition for the establishment of an Interim Maximum Allowable Concentration (IMAC) for a substance lacking a groundwater standard. In the absence of a groundwater standard for bentazon[1], an IMAC is proposed in this document. The IMAC was developed in accordance with the North Carolina Department of Environmental Quality (NCDEQ) Division of Water Resources Standard Operating Procedure for Establishing IMACs (NCDEQ, 2022).

Per the regulations [15A NCAC 02L.0202 (c)], the groundwater quality standard (GWQS) is the lowest of the following:

1. Systemic threshold concentration;
2. Concentration corresponding to an incremental lifetime cancer risk of 10^{-6};
3. Taste threshold limit value;
4. Odor threshold limit value;
5. Maximum contaminant level (MCL);
6. National secondary drinking water standard.

The regulations [15A NCAC 02L.0202 (c)] state that the following sources, in order of preference, be used in establishing the above levels:

1. The United States Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS).
2. Health Advisories (USEPA Office of Drinking Water).
3. Other health risk assessment data published by USEPA.
4. Other relevant, published health risk assessment data, and scientifically valid peer-reviewed published toxicological data.

Section 2 provides an overview of bentazon and a summary of available data. Risk-based GWQS are calculated in Section 3, and the proposed IMAC is presented in Section 4. References are provided in Section 5.

2. Bentazon Data

Bentazon (CAS No. 25057-89-0) is a registered post-emergence herbicide that has activity against broadleaf weeds and sedges. It is used for weed control in agricultural crops (e.g., beans, corn, peanuts,

[1] Also spelled “bentazone”. The spelling “bentazon” is used in this document, consistent with the spelling used in the USEPA IRIS file.

peas). Bentazon is a colorless to white crystalline powder and is odorless. The chemical structure and chemical properties are provided in **Attachment A** (PubChem, 2023).

An oral reference dose (RfD) of 0.03 milligrams per kilogram body weight per day (mg/kg-day) is available from IRIS (USEPA, 2023a) for bentazon. The RfD is based on a 52-week oral feeding study in beagle dogs. A lowest observed adverse effect level (LOAEL) of 13.1 mg/kg-day was identified for blood loss or blood coagulation in the intestinal tract of male beagle dogs. A no observed adverse effect level (NOAEL) of 3 mg/kg-day was established based on the study. USEPA applied uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies extrapolation to derive the RfD based on the NOAEL (3 mg/kg-day ÷ 100). USEPA assigned a confidence level of medium to the RfD. USEPA classified bentazon as a Group E chemical, with evidence of non-carcinogenicity (USEPA, 2023a). Therefore, a cancer slope factor was not derived. The IRIS file for bentazon is provided in **Attachment B**.

A drinking water lifetime health advisory level (HAL) of 0.2 milligrams per Liter (mg/L) is available from the USEPA (2018). The HAL is based on the RfD of 0.03 mg/kg-day established in IRIS and assumes daily exposure to bentazon in drinking water for a lifetime. USEPA has not established an MCL or a secondary drinking water standard (USEPA, 2023b). As noted previously, bentazon is odorless, and no odor or taste thresholds have been established.

3. Derivation of Risk-Based GWQS

A systemic threshold concentration for bentazon was derived in accordance with 15A NCAC 02L.0202(c)(1) as follows:

Derivation of Noncancer Systemic Threshold Concentration for Bentazon			
Parameter	**Value**	**Units**	**Notes/Source**
Oral Reference Dose (RfD)	0.03	mg/kg-day	IRIS (USEPA, 2023a)
Body Weight (WT)	70	kg	NCAC 02L.0202 (c)(1)
Relative Source Contribution (RSC)	0.2	unitless	NCAC 02L.0202 (c)(1). Value for organics
Water Ingestion Rate (WI)	2	L/day	NCAC 02L.0202 (c)(1)
Conversion Factor (CF)	1000	µg/mg	NCAC 02L.0202 (c)(1)
Noncancer Systemic Threshold Concentration	0.21	mg/L	[(RfD x WT x RSC)/WI] x CF

As bentazon is not classified as carcinogenic, there is no cancer slope factor and a GWQS for the cancer endpoint is not calculated.

4. Recommended IMAC

The table below summarizes the available thresholds for bentazon.

Selection of Proposed IMAC for Bentazon			
Parameter	**Value**	**Units**	**Notes/Source**
Noncancer Systemic Threshold Concentration	0.21	mg/L	Calculated above
Concentration corresponding to Cancer Risk 10^{-6}	--	--	Not carcinogenic
Taste Threshold Value	--	--	No threshold identified
Odor Threshold Value	--	--	Odorless; no threshold identified
Maximum Contaminant Level (MCL)	--	--	USEPA (2023b)
National Secondary Drinking Water Standard	--	--	USEPA (2023b)
Lifetime Health Advisory Level (HAL)	0.2	mg/L	USEPA (2018)
Proposed Interim Maximum Allowable Concentration (IMAC)	0.2	mg/L	Lowest value selected; USEPA HAL

Based on the review and calculations provided here, an IMAC of 0.2 mg/L is proposed for bentazon, based on USEPA's lifetime HAL.

5. References

NCDEQ. 2022. North Carolina Department of Environmental Quality, Division of Water Resources Standard Operating Procedure for Establishing Interim Maximum Allowable Concentrations (IMACs) per 15A NCAC 02L .0202 (c). Revised April.

PubChem. 2023. Bentazone. C10H12N2O3S. Compound Summary. https://pubchem.ncbi.nlm.nih.gov/compound/Bentazone Accessed 5/9/23.

USEPA. 2018. 2018 Edition of the Drinking Water Standards and Health Advisories Tables. EPA 822-F-18-001. Office of Water. USEPA. March.

USEPA. 2023a. Integrated Risk Information System (IRIS) database [online]. Environmental Criteria and Assessment Office, US Environmental Protection Agency, Washington, DC. https://www.epa.gov/iris. Accessed June 2023.

USEPA. 2023b. National Primary Drinking Water Regulations and Secondary Drinking Water Regulations. https://www.epa.gov/sdwa. Accessed June 2023.

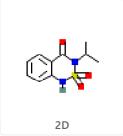
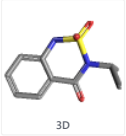
Attachment A

PubChem File

PubChem

COMPOUND SUMMARY

Bentazone

PubChem CID	2328
Structure	 2D  3D Find Similar Structures
Chemical Safety	 Irritant  Health Hazard Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula	$C_{10}H_{12}N_2O_3S$
Synonyms	Bentazone bentazon 25057-89-0 Basagran Bendioxide More...
Molecular Weight	240.28
Dates	Modify 2023-05-05 Create 2005-03-25

Bentazone is a benzothiadiazine that is 1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide substituted by an isopropyl group at position 3. It has a role as an environmental contaminant, a xenobiotic and a herbicide.

▸ ChEBI

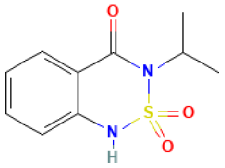
Bentazon is a chemical manufactured by BASF Chemicals for use in herbicides. It is categorized under the thiadiazine group of chemicals. Sodium bentazon is available commercially and appears slightly brown in colour. Bentazon has been classified by the EPA as a Group E chemical, because it is believed to be non-carcinogenic to humans (as based on testing conducted on animals). However, there are no studies or experiments that can determine toxic and/or carcinogenic effects of bentazon on humans.

▸ Toxin and Toxin Target Database (T3DB)

1 Structures

1.1 2D Structure

Chemical Structure Depiction



PubChem

1.2 3D Conformer

PubChem

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

2,2-dioxo-3-propan-2-yl-1*H*-2λ^6,1,3-benzothiadiazin-4-one

Computed by Lexichem TK 2.7.0 (PubChem release 2021.05.07)

PubChem

2.1.2 InChI

InChI=1S/C10H12N2O3S/c1-7(2)12-10(13)8-5-3-4-6-9(8)11-16(12,14)15/h3-7,11H,1-2H3

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.3 InChIKey

ZOMSMJKLGFBRBS-UHFFFAOYSA-N

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.4 Canonical SMILES

CC(C)N1C(=O)C2=CC=CC=C2NS1(=O)=O

Computed by OEChem 2.3.0 (PubChem release 2021.05.07)

PubChem

2.2 Molecular Formula

$C_{10}H_{12}N_2O_3S$

ILO International Chemical Safety Cards (ICSC)

C10H12N2O3S

Computed by PubChem 2.1 (PubChem release 2021.05.07)

PubChem

2.3 Other Identifiers

2.3.1 CAS

25057-89-0

CAS Common Chemistry; ChemIDplus; EPA Chemicals under the TSCA; EPA DSSTox; European Chemicals Agency (ECHA); FDA Global Substance Registration System (GSRS); Hazardous Substances Data Bank (HSDB); ILO International Chemical Safety Cards (ICSC); The National Institute for Occupational Safety and Health (NIOSH)

2.3.2 Related CAS

50723-80-3 (hydrochloride salt)

ChemIDplus

2.3.3 Deprecated CAS

12705-05-4, 21723-40-0, 58856-82-9

ChemIDplus

12705-05-4, 58856-82-9

EPA DSSTox

2.3.4 European Community (EC) Number

246-585-8

European Chemicals Agency (ECHA)

2.3.5 ICSC Number

0828

ILO International Chemical Safety Cards (ICSC)

2.3.6 RTECS Number

DK9900000

The National Institute for Occupational Safety and Health (NIOSH)

2.3.7 UNII

R4S7ZGZ9CT

FDA Global Substance Registration System (GSRS)

2.3.8 DSSTox Substance ID

DTXSID0023901

EPA DSSTox

2.3.9 Nikkaji Number

J1.875I

Japan Chemical Substance Dictionary (Nikkaji)

2.3.10 Wikipedia

Bentazon

Wikipedia

2.3.11 Wikidata

Q148937

Wikidata

2.3.12 Metabolomics Workbench ID

67425

Metabolomics Workbench

2.4 Synonyms

2.4.1 MeSH Entry Terms

Basagran
bentazon
bentazone
bentazone sodium

Medical Subject Headings (MeSH)

2.4.2 Depositor-Supplied Synonyms

Bentazone	BAS 3517H	Laddok	Bentazone [ISO]	3-Isopropyl-1H-benzo-2,1,3-thiadiazin-4-one 2
bentazon	BAS 3510	Pledge	CAS-25057-89-0	SpecPlus_000462
25057-89-0	BAS 351-07H	Basagran-plus	CCRIS 6977	3-Isopropyl-2,1,3-benzothiadiazinon-(4)-2,2-d
Basagran	R4S7ZGZ9CT	Graminon-plus	BAS 351-H	BENTAZON [MI]
Bendioxide	3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide	Basagran KV	HSDB 3430	BENTAZONE [HSDB]
Leader	1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-isopropyl-, 2,2-dioxide	3-(1-METHYLETHYL)-1H-2,1,3-BENZOTHIADIAZIN-4(3H)-ONE 2,2-DIOXIDE	EINECS 246-585-8	1H-2,1,3-Benzothiadiazin-4(3H)-one-2,2-dioxi
Basagran 480	CHEBI:3018	Bentazon [ANSI]	UNII-R4S7ZGZ9CT	Spectrum2_001889
Pentazone	DTXSID0023901	DTXCID503901	EPA Pesticide Chemical Code 275200	Spectrum3_000831
1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-, 2,2-dioxide	3-Isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide	Caswell No. 509C	BRN 0530220	Spectrum4_000671
BAS 351H	3-Isopropyl-2,1,3-benzothiadiazinon-(4)-2,2-dioxid	Adagio	2,2-dioxo-3-propan-2-yl-1H-2?^{6},1,3-benzothiadiazin-4-one	Spectrum5_001976
BAS 3510H	Bentazone 10 microg/mL in Acetonitrile	Bentazone [BSI:ISO]	3-Isopropyl-4H-2,1,3-benzothiadiazin-4-one 2,2-dioxide	3-(1-Methylethyl)-(1H)-2,1,3-benzothiadiazin-4
BAS 3512H	Bentazone 100 microg/mL in Acetonitrile	3-isopropyl-1H-benzo[c][1,2,6]thiadiazin-4(3H)-one 2,2-dioxide	Spectrum_001851	Oprea1_558180

PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	240.28	Computed by PubChem 2.1 (PubChem release 2021.05.07)
XLogP3	2.8	Computed by XLogP3 3.0 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	1	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	4	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Rotatable Bond Count	1	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Exact Mass	240.05686342	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Monoisotopic Mass	240.05686342	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	74.9 Å^2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Heavy Atom Count	16	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	385	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.05.07)

PubChem

3.2 Experimental Properties

3.2.1 Physical Description

Colorless to white solid; [ICSC]

Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

COLOURLESS-TO-WHITE CRYSTALLINE POWDER.

ILO International Chemical Safety Cards (ICSC)

3.2.2 Color/Form

Colorless crystals; tech. is an ochre-yellow solid [

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

Hazardous Substances Data Bank (HSDB)

White, crystalline powder

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 185

Hazardous Substances Data Bank (HSDB)

3.2.3 Odor

Odorless

Spencer, E. Y. Guide to the Chemicals Used in Crop Protection. 7th ed. Publication 1093. Research Institute, Agriculture Canada, Ottawa, Canada: Information Canada, 1982., p. 38

Hazardous Substances Data Bank (HSDB)

3.2.4 Melting Point

139.7 °C

Haynes, W.M. (ed.). CRC Handbook of Chemistry and Physics. 95th Edition. CRC Press LLC, Boca Raton: FL 2014-2015, p. 3-34

▸ Hazardous Substances Data Bank (HSDB)

Decomposition temp: 200 °C

Ahrens, W.H. Herbicide Handbook of the Weed Science Society of America. 7th ed. Champaign, IL: Weed Science Society of America, 1994., p. 33

▸ Hazardous Substances Data Bank (HSDB)

137-139 °C

▸ ILO International Chemical Safety Cards (ICSC)

3.2.5 Solubility

Solubility: xylene < 1 g/100 g (at 20 °C). /Technical bentazon/

Farm Chemicals Handbook 2000. Willoughby, Ohio: Meister 2000., p. C 49

▸ Hazardous Substances Data Bank (HSDB)

In water, 500 mg/L at 20 °C

Yalkowsky, S.H., He, Yan, Jain, P. Handbook of Aqueous Solubility Data Second Edition. CRC Press, Boca Raton, FL 2010, p. 680

▸ Hazardous Substances Data Bank (HSDB)

In water 570 mg/L (pH 7, 20 °C)

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

In acetone 1507, ethanol 861, ethyl acetate 650, diethyl ether 616, chloroform 180, benzene 33, cyclohexane 0.2 (all in g/kg, 20 °C)

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

Solubility at 20 °C in xylene <1 g/100g; cyclohexanone approx 18 g/100g

Farm Chemicals Handbook 2000. Willoughby, Ohio: Meister 2000., p. C 49

▸ Hazardous Substances Data Bank (HSDB)

Solubility in water: none

▸ ILO International Chemical Safety Cards (ICSC)

3.2.6 Density

1.41 at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.7 Vapor Pressure

0.00000345 [mmHg]

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

4.05X10-8 mm Hg at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

Vapor pressure, Pa at 20 °C:

ILO International Chemical Safety Cards (ICSC)

3.2.8 LogP

log Kow = 2.34

Saito H et al; Chemosphere 27:1553-60 (1993)

Hazardous Substances Data Bank (HSDB)

-0.46

ILO International Chemical Safety Cards (ICSC)

3.2.9 Stability/Shelf Life

Stable under recommended storage conditions.

*Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

3.2.10 Decomposition

When heated to decomposition it emits very toxic fumes of /sulfur oxides and nitrogen oxides/.

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2443

Hazardous Substances Data Bank (HSDB)

200 °C

ILO International Chemical Safety Cards (ICSC)

3.2.11 Corrosivity

Not corrosive

Ahrens, W.H. Herbicide Handbook of the Weed Science Society of America. 7th ed. Champaign, IL: Weed Science Society of America, 1994., p. 33

Hazardous Substances Data Bank (HSDB)

3.2.12 Dissociation Constants

pKa = 3.3 at 24 °C

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 185

Hazardous Substances Data Bank (HSDB)

Dissociation constant: pKa = 2.92 at 20 °C

Comer J et al; SAR and QSAR Environ Research 3: 307-313 (1995)

Hazardous Substances Data Bank (HSDB)

3.2.13 Collision Cross Section

147.66 Å^2 $[M-H]^-$

145.63 Å^2 $[M+H]^+$

*S61 | UJICCSLIB | Collision Cross Section (CCS) Library from UJI | **DOI:10.5281/zenodo.3549476***

NORMAN Suspect List Exchange

3.2.14 Kovats Retention Index

Standard non-polar	1926

NIST Mass Spectrometry Data Center

3.2.15 Other Experimental Properties

Slightly brown solid /Technical bentazon/

Farm Chemicals Handbook 1984. Willoughby, Ohio: Meister Publishing Co., 1984., p. C-25

▸ Hazardous Substances Data Bank (HSDB)

Kow logP = 0.77 (pH 5), -0.46 (pH 7), -0.55 (pH 9)

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

Very resistant to hydrolysis in both acidic and alkaline media. Decomposed by sunlight

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.16 Chemical Classes

Pesticides -> Herbicides, Other

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

3.3 SpringerMaterials Properties

Fusion temperature
Melting temperature
Phase transition
Transition enthalpy

▸ SpringerMaterials

4 Spectral Information

4.1 1D NMR Spectra

1D NMR Spectra	NMRShiftDB Link

NMRShiftDB

4.1.1 1H NMR Spectra

Spectra ID	2305
Instrument Type	JEOL
Frequency	400 MHz
Solvent	CDCl3
Shifts [ppm]:Intensity	1.56:992.00, 1.58:1000.00, 4.98:19.00, 5.00:49.00, 5.01:66.00, 5.03:48.00, 5.05:19.00, 7.07:68.00, 7.07:79.00, 7.07:80.00, 7.07:90.00, 7.09:74.00, 7.09:87.00, 7.09:90.00, 7.09:93.00, 7.31:56.00, 7.33:66.00, 7.33:83.00, 7.33:86.00, 7.35:66.00, 7.35:69.00, 7.54:67.00, 7.54:71.00, 7.56:70.00, 7.56:74.00, 7.56:76.00, 7.58:52.00, 7.84:37.00, 8.12:76.00, 8.12:85.00, 8.12:93.00, 8.13:73.00, 8.14:73.00, 8.14:83.00, 8.14:84.00, 8.15:69.00
Thumbnail	

Human Metabolome Database (HMDB)

4.1.2 13C NMR Spectra

Showing 2 of 3 View More

Spectra ID	3009
Instrument Type	JEOL
Frequency	100.40 MHz
Solvent	CDCl3
Shifts [ppm]:Intensity	120.27:325.00, 120.39:182.00, 125.71:365.00, 130.28:375.00, 134.62:369.00, 135.94:215.00, 162.35:231.00, 20.69:1000.00, 49.24:370.00
Thumbnail	

Human Metabolome Database (HMDB)

Source of Sample	W. Bremser BASF Ludwigshafen (1973)
Copyright	Copyright © 1980, 1981-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

4.2 Mass Spectrometry

4.2.1 GC-MS

Showing 2 of 7 View More

MoNA ID	JP010425
MS Category	Experimental
MS Type	GC-MS
MS Level	MS1
Instrument	JEOL JMS-DX-303
Instrument Type	EI-B
Ionization Mode	positive
Top 5 Peaks	198 99.99 119 79.30 161 34.27 225 26.33 182 24.14
SPLASH	splash10-00kb-2910000000-678111d259a160fc4775
Thumbnail	
License	CC BY-NC-SA

MassBank of North America (MoNA)

NIST Number	53842
Library	Main library
Total Peaks	50
m/z Top Peak	198
m/z 2nd Highest	119
m/z 3rd Highest	161
Thumbnail	

NIST Mass Spectrometry Data Center

4.2.2 MS-MS

Showing 2 of 6 View More

Spectra ID	2226874
Ionization Mode	Negative
SPLASH	splash10-001i-0900000000-6f00314bbc0751c45027
Top 5 Peaks	132.0329 100 133.0407 38.21 197.0026 11.25 117.0458 7.19 195.9948 5.56
Thumbnail	

Human Metabolome Database (HMDB)

Spectra ID	2227003
Ionization Mode	Positive
SPLASH	splash10-0002-0900000000-e2ad6071873a3333967a
Top 5 Peaks	199.0172 100

	135.0554 42.73 120.0444 25.85 107.0602 23.34
Thumbnail	

Human Metabolome Database (HMDB)

4.2.3 LC-MS

Showing 2 of 59 View More

Accession ID	MSBNK-ACES_SU-AS000229
Authors	ACESx, Jonathan W. Martin Group
Instrument	QExactive Orbitrap HF-X (Thermo Scientific)
Instrument Type	LC-ESI-QFT
MS Level	MS2
Ionization Mode	NEGATIVE
Ionization	ESI
Collision Energy	Ramp 20%-70% (nominal)
Fragmentation Mode	HCD
Column Name	Waters; Acquity UPLC BEH C18, 2.1 x 100 mm, 1.7 um, Waters
Retention Time	8.3618
Precursor m/z	239.0498
Top 5 Peaks	239.05004 999 132.03291 300 133.04105 126 197.00261 66 117.04607 32
SPLASH	splash10-000i-0590000000-53d5b2487f7481aa9fde
Thumbnail	

License	CC BY

MassBank Europe

Accession ID	MSBNK-Athens_Univ-AU231301
Authors	Nikiforos Alygizakis, Katerina Galani, Nikolaos Thomaidis, University of Athens
Instrument	Bruker maXis Impact
Instrument Type	LC-ESI-QTOF
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	10 eV
Fragmentation Mode	CID
Column Name	Acclaim RSLC C18 2.2um, 2.1x100mm, Thermo
Retention Time	5.478 min
Precursor m/z	241.0641
Precursor Adduct	[M+H]+
Top 5 Peaks	199.0161 999 200.0178 95 241.0632 81 201.0123 59 197.0286 25
SPLASH	splash10-0002-0920000000-24421ad3c5f9ad621c89
Thumbnail	
License	CC BY

MassBank Europe

4.2.4 Other MS

Accession ID	MSBNK-ACES_SU-AS000034
Authors	ACESx, Jonathan W. Martin Group
Instrument	QExactive Orbitrap HF-X (Thermo Scientific)
Instrument Type	LC-APCI-QFT
MS Level	MS2
Ionization Mode	NEGATIVE
Ionization	APCI
Collision Energy	Ramp 20%-70% (nominal)
Fragmentation Mode	HCD
Column Name	Waters; Acquity UPLC BEH C18, 2.1 x 100 mm, 1.7 um, Waters
Retention Time	8.3724
Precursor m/z	239.0497

Top 5 Peaks	239.04985 999 132.03337 287 197.00301 167 175.08772 146 240.0528 112
SPLASH	splash10-000i-0690000000-da1aa42e8c996b940782
Thumbnail	
License	CC BY

MassBank Europe

Accession ID	MSBNK-Fac_Eng_Univ_Tokyo-JP010425
Authors	UOEH
Instrument	JEOL JMS-DX-303
Instrument Type	EI-B
MS Level	MS
Ionization Mode	POSITIVE
Ionization	ENERGY 70 eV
Top 5 Peaks	198 999 119 793 161 343 225 263 182 241
SPLASH	splash10-00kb-2910000000-678111d259a160fc4775
Thumbnail	
License	CC BY-NC-SA

MassBank Europe

4.3 IR Spectra

4.3.1 FTIR Spectra

Technique	KBr WAFER
Source of Sample	Riedel-De Haen AG
Copyright	Copyright © 1980, 1981-2021 John Wiley & Sons, Inc. All Rights Reserved.

Thumbnail

SpectraBase

Instrument Name	Bruker IFS 112
Technique	KBr-Pellet
Copyright	Copyright © 1989, 1990-2021 Wiley-VCH Verlag GmbH & Co. KGaA. All Rights Reserved.

Thumbnail

SpectraBase

4.4 Other Spectra

Intense mass spectral peaks: 198 m/z (100%), 119 m/z (96%), 161 m/z (39%), 92 m/z (31%)

Hites, R.A. Handbook of Mass Spectra of Environmental Contaminants. Boca Raton, FL: CRC Press Inc., 1985., p. 274

Hazardous Substances Data Bank (HSDB)

5 Related Records

5.1 Related Compounds with Annotation

PubChem

5.2 Related Compounds

Same Connectivity	6 Records
Same Parent, Connectivity	25 Records
Same Parent, Exact	20 Records
Mixtures, Components, and Neutralized Forms	120 Records
Similar Compounds	186 Records
Similar Conformers	2,140 Records

PubChem

5.3 Substances

5.3.1 Related Substances

All	364 Records
Same	152 Records
Mixture	212 Records

PubChem

5.3.2 Substances by Category

PubChem

5.4 Entrez Crosslinks

PubMed	126 Records
Taxonomy	1 Record
OMIM	1 Record
Gene	1 Record

PubChem

5.5 Associated Chemicals

Bentazone-sodium; 50723-80-3

Hazardous Substances Data Bank (HSDB)

5.6 NCBI LinkOut

NCBI

6 Chemical Vendors

PubChem

7 Agrochemical Information

7.1 Agrochemical Category

Herbicide

- EPA Pesticide Ecotoxicity Database

Pesticide active substances

- EU Pesticides Database

Herbicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | DOI:10.5281/zenodo.3862688

- NORMAN Suspect List Exchange

7.2 Agrochemical Transformations

Bentazone has known environmental transformation products that include N-methyl bentazone and 2-amino-N-isopropylbenzamide.

S78 | SLUPESTTPS | Pesticides and TPs from SLU, Sweden | DOI:10.5281/zenodo.4687924

- NORMAN Suspect List Exchange

Bentazone has known environmental transformation products that include 8-OH-bentazone, 8-chloro-bentazone, 6-chloro-bentazone, N-methyl Bentazone, 8-bromo-bentazone, 6-bromo-bentazone, and 6-OH-bentazone.

S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 | DOI:10.5281/zenodo.3544759

- NORMAN Suspect List Exchange

7.3 EU Pesticides Data

Active Substance	bentazone
Status	Date of Approval: 01/06/2018 Expiration of Approval: 31/05/2025 [Reg. (EC) No 1107/2009]
Legislation	00/68/EC, 2010/77/EU, Reg. (EU) 2015/1885, Reg. (EU) 2016/549, Reg. (EU) 2017/841, Reg. (EU) 2018/660, Reg. (EU) 2020/1093, Reg. (EU) No 540/2011
ADI	0.09 mg/kg bw/day [Reg. (EU) 2018/660]
ARfD	1.0 mg/kg bw [Reg. (EU) 2018/660]
AOEL	0.13 mg/kg bw/day [Reg. (EU) 2018/660]

- EU Pesticides Database

7.4 USDA Pesticide Data Program

Pesticide	Bentazon
Carrots	EPA tolerance level: NT
Eggplant	EPA tolerance level: NT
Kiwi Fruit	EPA tolerance level: NT
Summer Squash	EPA tolerance level: NT
Tangerines	EPA tolerance level: NT
Tomato Paste	EPA tolerance level: NT

- USDA Pesticide Data Program

8 Pharmacology and Biochemistry

8.1 MeSH Pharmacological Classification

Herbicides

Pesticides used to destroy unwanted vegetation, especially various types of weeds, grasses (POACEAE), and woody plants. Some plants develop HERBICIDE RESISTANCE. (See all compounds classified as Herbicides.)

Medical Subject Headings (MeSH)

8.2 Absorption, Distribution and Excretion

Toxicokinetic studies performed on mice, rats and rabbits indicate that bentazone is rapidly and almost completely absorbed via the oral route (> 99%), and maximum blood concentrations of radioactivity are achieved in approximately 15 minutes at low doses (4 mg/kg bw) and by 1 hour at high doses (200 mg/kg bw). Administration of bentazone either as the sodium salt or as the free acid did not result in any significant differences in absorption. There was no evidence of penetration into the central nervous system or spinal cord, and elimination from other tissues was rapid, with no indication of bioaccumulation. Elimination was almost exclusively via the urine (approximately 91% within 24 hours); 5 days after dosing, less than 2% was found in feces and less than 0.02% in expired air. Biliary excretion of radioactivity was minimal. No significant differences were found in absorption and elimination among the different species investigated (rat, rabbit, mouse).

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.86 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

The dermal penetration of [14C]bentazone sodium salt (batch no. 210-2201, radiochemical purity 97.3%) through human skin was assessed by a single topical application of about 4933, 49.3 or 8.22 ug/sq cm of active ingredient formulated in BAS 351 32 H to split thickness skin membranes mounted on Franz-type diffusion cells. The doses represent the formulation concentrate or two representative spray dilutions (1:100 and 1:600) for field use, respectively. The study was performed using five diffusion cells per dose. ... It can be concluded that in vitro dermal penetration of bentazone formulated as an aqueous soluble (liquid) concentrate formulation of bentazone sodium through human skin is appropriately calculated as per cent absorbed dose. Considering the amount of radiolabeled substance associated with the skin (remaining skin and tape strips 3-6) after washing as absorbable and combining this with the absorbed amount detected in the receptor, the extent of dermal penetration through human epidermis is about 0.06% for the concentrate, 1.31% for the 1:100 spray strength dilution and 1.23% for the 1:600 dilution. /Bentazone sodium salt/

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.83-5 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

A case of fatal suicidal bentazone poisoning was presented along with a description of the different analytical methods involved. A 56-year-old farmer was examined by the family doctor 1 hour after voluntarily ingesting 500 mL of FIGHTER (about 250 g bentazone). He presented a Glasgow score of 15, polypnea, diarrhea and vomiting. During transport by ambulance to the hospital, he tossed, sweated and suddenly presented breathing difficulty followed by heart failure. The patient died within 2 hours post-ingestion. Blood and urine samples were taken just before death. Bentazone plasma and urine levels were 1500 and 1000 mg/L, respectively.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.86 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

A 59-year-old woman who intentionally ingested 100-200 mL Basagran (about 50-100 g bentazone) was taken to the hospital with cardiac arrest 2 days after she had consumed the herbicide. During this period, she suffered vomiting, urination and diarrhoea, and she was drowsy with a muddled speech. Biological samples obtained at the autopsy were analysed, and the presence of bentazone, alcohol and an active metabolite of citalopram was detected. Blood concentrations of bentazone, alcohol and desmethyl-citalopram were 625 mg/kg, 0.62 g/L and 0.03 mg/kg, respectively.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.86 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

8.3 Metabolism/Metabolites

The metabolism of bentazone was investigated in a number of toxicokinetic studies following oral (rat and rabbit) or intravenous administration (mouse) ... . Bentazone was only poorly metabolized, with the parent compound being the predominant excretion product. Only small amounts of 6-hydroxybentazone and 8-hydroxybentazone could be detected. In rats, rabbits and mice, no conjugated products were found.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.37 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

6-Hydroxybentazone and 8-hydroxybentazone are major plant metabolites of bentazone. Because crops of treated plants can be consumed by humans, farm animals or pets, an exposure to both of these compounds might be expected in principle. Although both metabolites have been demonstrated to be formed in mammals and therefore can be regarded as included in toxicological testing of the parent compound, specific toxicological studies were performed. It has been shown that the 8-hydroxy and 6-hydroxy metabolites of bentazone are of comparable toxicity by the oral route of administration and are both less toxic than the parent compound. Additionally, both metabolites were negative in the Ames assay for the potential to induce point mutations in bacteria. As it is unlikely that a hydroxy group shift in the bentazone ring system dramatically changes the toxicity, it was decided to perform further investigations on 8-hydroxybentazone as a reference substance. Therefore, 8-hydroxybentazone was investigated in a subchronic feeding study, in several mutagenicity studies and in a prenatal developmental study. These investigations revealed that the metabolites have no mutagenic or teratogenic potential and are less toxic than the parent substance.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.80 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

In studies with soybeans [Glycine max (Leguminatae) Merr.] and navy beans (Phaseolus vulgaris Leguminatae), four unidentified conjugates were observed. After foliar or root absorption, bentazon was rapidly metabolized by soybeans with hydroxylation at the 6 and 8 position. These were conjugated. Analysis of soybean field samples showed hydroxylation of bentazon in early growth stages.

Menzie, C.M. Metabolism of Pesticides-Update III. Special Scientific Report- Wildlife No. 232. Washington, DC: U.S.Department of the Interior, Fish and Wildlife Service, 1980., p. 61

Hazardous Substances Data Bank (HSDB)

Although absorption and translocation of bentazon was not markedly different in resistant rice and susceptible C. serotinus, metabolism differed markedly. In rice, there was 80% metabolism of absorbed bentazon within 24 hr and 85% conversion to a major water soluble metabolite within 7 days. In C. serotinus, there was only 25-50% metabolism of bentazon in 7 days. Similar results were obtained with other resistant and susceptible plant species indicating that ability to metabolize this compound is the primary mechanism of selectivity. The primary metabolite in rice was

identified by GC-MS, NMR and IR as 6-(bentazon)-O-beta-glucopyranoside. Other studies showed that the 6- and **8-hydroxybentazon** were formed in about equal amounts in soybeans and that the 6-hydroxy analog predominates in wheat, rice, peanuts, Senecio sp., and Chenopodium sp.

Menzie, C.M. Metabolism of Pesticides-Update III. Special Scientific Report- Wildlife No. 232. Washington, DC: U.S.Department of the Interior, Fish and Wildlife Service, 1980., p. 61

▸ Hazardous Substances Data Bank (HSDB)

For more Metabolism/Metabolites (Complete) data for Bentazon (8 total), please visit the **HSDB record page**.

▸ Hazardous Substances Data Bank (HSDB)

8.4 Mechanism of Action

Inhibition of photosynthesis at photosystem II.

Crop Protection Handbook Volume 100, Meister Media Worldwide, Willoughby, OH 2014, p. 130

▸ Hazardous Substances Data Bank (HSDB)

8.5 Transformations

▸ NORMAN Suspect List Exchange

9 Use and Manufacturing

9.1 Uses

EPA CPDat Chemical and Product Categories

The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products, Scientific Data, volume 5, Article number: 180125 (2018), DOI:10.1038/sdata.2018.125

EPA Chemical and Products Database (CPDat)

Sources/Uses

Used as a post-emergence herbicide with activity against a wide range of broadleaf weeds, as well as yellow nutsedge; [HSDB]

Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

Industrial Processes with risk of exposure

Farming (Pesticides) [Category: Industry]

Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

For bentazon (USEPA/OPP Pesticide Code: 275200) ACTIVE products with label matches. /SRP: Registered for use in the USA but approved pesticide uses may change periodically and so federal, state and local authorities must be consulted for currently approved uses./

National Pesticide Information Retrieval System's Database on Bentazon (25057-89-0). Available from, as of October 31, 2017: https://npirspublic.ceris.purdue.edu/ppis/

Hazardous Substances Data Bank (HSDB)

Herbicide

Crop Protection Handbook Volume 100, Meister Media Worldwide, Willoughby, OH 2014, p. 130

Hazardous Substances Data Bank (HSDB)

A selective herbicide to control many broadleaf weeds and yellow nutsedge. A postemergence contact spray, so thorough coverage is essential.

Crop Protection Handbook Volume 100, Meister Media Worldwide, Willoughby, OH 2014, p. 130

Hazardous Substances Data Bank (HSDB)

This is a man-made compound that is used as a pesticide.

Toxin and Toxin Target Database (T3DB)

9.1.1 Use Classification

Agrochemicals -> Pesticides

EU Pesticides Database

Pharmaceuticals

S72 | NTUPHTW | Pharmaceutically Active Substances from National Taiwan University | DOI:10.5281/zenodo.3955664

NORMAN Suspect List Exchange

Herbicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | DOI:10.5281/zenodo.3862688

NORMAN Suspect List Exchange

Environmental transformation -> Pesticides (parent, predecessor)

S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 | DOI:10.5281/zenodo.3544759

NORMAN Suspect List Exchange

9.2 Methods of Manufacturing

Bentazone can be made by reaction of methylanthralinate with **isopropylsulfamoyl chloride**.

Muller F, Applebyki AP; Ullmann's Encyclopedia of Industrial Chemistry 7th ed. (1999-2017). NY, NY: John Wiley & Sons; Weed Control, 2. Individual Herbicides. Online Posting Date: September 15, 2010

Hazardous Substances Data Bank (HSDB)

... Made by the reaction of **anthranilic acid** with **isopropylsulfamoyl chloride** to give N-(isopropylsulfamoyl) anthranilic acid which is then cyclized with **phosgene** to give bentazon .

Sittig, M. (ed.) Pesticide Manufacturing and Toxic Materials Control Encyclopedia. Park Ridge, NJ: Noyes Data Corporation. 1980., p. 88

Hazardous Substances Data Bank (HSDB)

Preparation: A. Zeidler et al., South Africa patent 6705164; eidem, United States of America patent 3708277 (1968, 1973 both to BASF).

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 185

Hazardous Substances Data Bank (HSDB)

9.3 Formulations/Preparations

UPI Bentazon Technical (United **Phosphorus**, Inc.): Active ingredient: bentazon 98.6%.

National Pesticide Information Retrieval System's Database on Bentazon (25057-89-0). Available from, as of October 31, 2017: https://npirspublic.ceris.purdue.edu/ppis/

Hazardous Substances Data Bank (HSDB)

Bentazon Technical (Sharda Cropchem Limited): Active ingredient: bentazon 98.6%.

National Pesticide Information Retrieval System's Database on Bentazon (25057-89-0). Available from, as of October 31, 2017: https://npirspublic.ceris.purdue.edu/ppis/

Hazardous Substances Data Bank (HSDB)

Sharda Bentazon 5L (Sharda USA LLC): Active ingredient: bentazon 53.0%%.

National Pesticide Information Retrieval System's Database on Bentazon (25057-89-0). Available from, as of October 31, 2017: https://npirspublic.ceris.purdue.edu/ppis/

Hazardous Substances Data Bank (HSDB)

Bentazon Technical (Redeagle International LLC): Active ingredient: bentazon 98.9%.

National Pesticide Information Retrieval System's Database on Bentazon (25057-89-0). Available from, as of October 31, 2017: https://npirspublic.ceris.purdue.edu/ppis/

Hazardous Substances Data Bank (HSDB)

For more Formulations/Preparations (Complete) data for Bentazon (7 total), please visit the **HSDB record page**.

Hazardous Substances Data Bank (HSDB)

9.4 U.S. Imports

In the period 1970 to 1980, the US imported over 500 metric tons of bentazon.

Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed., Volumes 1-26. New York, NY: John Wiley and Sons, 1978-1984., p. 12 297-51(1980)

Hazardous Substances Data Bank (HSDB)

9.5 General Manufacturing Information

EPA TSCA Commercial Activity Status

1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-, 2,2-dioxide: ACTIVE

https://www.epa.gov/tsca-inventory

- EPA Chemicals under the TSCA

The WHO Recommended Classification of Pesticides by Hazard identifies bentazone (technical grade) as Class II: moderately hazardous; Main Use: herbicide.

WHO International Programme on Chemical Safety; The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009 p.24 (2010)

- Hazardous Substances Data Bank (HSDB)

10 Identification

10.1 Analytic Laboratory Methods

Method: USGS-NWQL O-2060-01; Procedure: high performance liquid chromatography-mass spectrometry; Analyte: bentazon; Matrix: water; Detection Limit: 0.0055 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Bentazon (25057-89-0). Available from, as of November 2, 2017: https://www.nemi.gov

Hazardous Substances Data Bank (HSDB)

Method: USGS-NWQL O-1131-95; Procedure: high performance liquid chromatography; Analyte: bentazon; Matrix: natural water; Detection Limit: 0.014 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Bentazon (25057-89-0).

Hazardous Substances Data Bank (HSDB)

Method: EPA-TSC/NERL 515.1; Procedure: gas chromatography with an electron capture detector; Analyte: bentazon; Matrix: ground water and finished drinking water; Detection Limit: 0.11 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Bentazon (25057-89-0). Available from, as of November 2, 2017: https://www.nemi.gov

Hazardous Substances Data Bank (HSDB)

Method: EPA-RCA 8151A; Procedure: gas chromatography with an electron capture detector; Analyte: bentazon; Matrix: water, soil, and waste samples; Detection Limit: 0.2 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Bentazon (25057-89-0). Available from, as of November 2, 2017: https://www.nemi.gov

Hazardous Substances Data Bank (HSDB)

For more Analytic Laboratory Methods (Complete) data for Bentazon (17 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

11 Safety and Hazards

11.1 Hazards Identification

11.1.1 GHS Classification

Showing 1 of 4 View More

Pictogram(s)	 Irritant Health Hazard
Signal	Warning
GHS Hazard Statements	H302: Harmful if swallowed [Warning Acute toxicity, oral] H317: May cause an allergic skin reaction [Warning Sensitization, Skin] H319: Causes serious eye irritation [Warning Serious eye damage/eye irritation] H361d: Suspected of damaging the unborn child [Warning Reproductive toxicity]
Precautionary Statement Codes	P203, P261, P264, P264+P265, P270, P272, P280, P301+P317, P302+P352, P305+P351+P338, P318, P321, P330, P333+P313, P337+P317, P362+P364, P405, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)

▸ EU REGULATION (EC) No 1272/2008

11.1.2 Hazard Classes and Categories

Showing 2 of 3 View More

Repr. 2

Acute Tox. 4

Eye Irrit. 2

Skin Sens. 1

▸ EU REGULATION (EC) No 1272/2008

Acute Tox. 4 (100%)

Skin Sens. 1 (100%)

Eye Irrit. 2 (100%)

Repr. 2 (32.14%)

Aquatic Chronic 3 (67.86%)

▸ European Chemicals Agency (ECHA)

11.1.3 Fire Hazards

Liquid formulations containing organic solvents may be flammable. Gives off irritating or toxic fumes (or gases) in a fire. Risk of fire and explosion if formulations contain flammable/explosive solvents.

▸ ILO International Chemical Safety Cards (ICSC)

11.1.4 Hazards Summary

An eye irritant; [ICSC] A mucous membrane irritant; [HSDB] May cause skin sensitization; [eChemPortal: ESIS] An eye irritant; [MSDSonline] Not likely to be carcinogenic to humans (Group NL); [EPA]

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

11.1.5 Skin, Eye, and Respiratory Irritations

Bentazone is not a skin irritant but was a moderate eye irritant in rabbits.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.38 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

▸ Hazardous Substances Data Bank (HSDB)

Irritating to eyes and mucous membranes.

Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-340

- Hazardous Substances Data Bank (HSDB)

11.2 First Aid Measures

11.2.1 Inhalation First Aid

Fresh air, rest. Refer for medical attention.

- ILO International Chemical Safety Cards (ICSC)

11.2.2 Skin First Aid

Remove contaminated clothes. Rinse and then wash skin with water and soap.

- ILO International Chemical Safety Cards (ICSC)

11.2.3 Eye First Aid

First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.

- ILO International Chemical Safety Cards (ICSC)

11.2.4 Ingestion First Aid

Give one or two glasses of water to drink. Refer for medical attention .

- ILO International Chemical Safety Cards (ICSC)

11.3 Fire Fighting

Use water spray, powder, foam, carbon dioxide.

- ILO International Chemical Safety Cards (ICSC)

11.3.1 Fire Fighting Procedures

Suitable extinguishing media: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

*Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: **https://www.sigmaaldrich.com/safety-center.html***

- Hazardous Substances Data Bank (HSDB)

Wear self contained breathing apparatus for fire fighting if necessary.

*Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: **https://www.sigmaaldrich.com/safety-center.html***

- Hazardous Substances Data Bank (HSDB)

11.4 Accidental Release Measures

11.4.1 Spillage Disposal

Do NOT wash away into sewer. Sweep spilled substance into covered containers. If appropriate, moisten first to prevent dusting. Carefully collect remainder. Then store and dispose of according to local regulations. Personal protection: chemical protection suit including self-contained breathing apparatus.

- ILO International Chemical Safety Cards (ICSC)

11.4.2 Cleanup Methods

ACCIDENTAL RELEASE MEASURES: Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Evacuate personnel to safe areas. Avoid breathing dust. Environmental precautions: Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided. Methods and materials for containment and cleaning up: Pick up and arrange disposal without creating dust. S weep up and shovel. Keep in suitable, closed containers for disposal.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

11.4.3 Disposal Methods

SRP: Recycle any unused portion of the material for its approved use or return it to the manufacturer or supplier. Ultimate disposal of the chemical must consider: the material's impact on air quality; potential migration in air, soil or water; effects on animal, aquatic and plant life; and conformance with environmental and public health regulations. If it is possible or reasonable use an alternative chemical product with less inherent propensity for occupational harm/injury/toxicity or environmental contamination.

Hazardous Substances Data Bank (HSDB)

Product: Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material; Contaminated packaging: Dispose of as unused product.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Group I Containers: Combustible containers from organic or metallo-organic pesticides (except organic mercury, lead, cadmium, or arsenic compounds) should be disposed of in pesticide incinerators or in specified landfill sites. /Organic or metallo-organic pesticides/

40 CFR 165.9(a) (7/1/91)

Hazardous Substances Data Bank (HSDB)

Group II Containers: Non-combustible containers from organic or metallo-organic pesticides (except organic mercury, lead, cadmium, or arsenic compounds) must first be triple-rinsed. Containers that are in good condition may be returned to the manufacturer or formulator of the pesticide product, or to a drum reconditioner for reuse with the same type of pesticide product, if such reuse is legal under Department of Transportation regulations (eg 49 CFR 173.28). Containers that are not to be reused should be punctured ... and transported to a scrap metal facility for recycling, disposal or burial in a designated landfill. /Organic or metallo-organic pesticides/

40 CFR 165.9(b) (7/1/91)

Hazardous Substances Data Bank (HSDB)

11.4.4 Preventive Measures

ACCIDENTAL RELEASE MEASURES: Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Evacuate personnel to safe areas. Avoid breathing dust. Environmental precautions: Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Precautions for safe handling: Avoid contact with skin and eyes. Avoid formation of dust and aerosols. Provide appropriate exhaust ventilation at places where dust is formed.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Appropriate engineering controls: Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

For more Preventive Measures (Complete) data for Bentazon (6 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

11.5 Handling and Storage

11.5.1 Safe Storage

Provision to contain effluent from fire extinguishing. Separated from food and feedstuffs.

ILO International Chemical Safety Cards (ICSC)

11.5.2 Storage Conditions

Keep container tightly closed in a dry and well-ventilated place.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

11.6 Exposure Control and Personal Protection

11.6.1 Inhalation Risk

Evaporation at 20 °C is negligible; a harmful concentration of airborne particles can, however, be reached quickly on spraying or when dispersed, especially if powdered.

ILO International Chemical Safety Cards (ICSC)

11.6.2 Effects of Short Term Exposure

The substance is irritating to the eyes.

ILO International Chemical Safety Cards (ICSC)

11.6.3 Acceptable Daily Intakes

FAO/WHO ADI: 0.1 mg/kg bw

FAO/WHO; Pesticide Residues in Food - 1991. Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. Geneva, September 16-22, 1991. Evaluations Part 1 - Residues. p.631 FAO Plant & Prod Protect Paper 113/1 (1992)

Hazardous Substances Data Bank (HSDB)

11.6.4 Allowable Tolerances

Tolerances are established for the combined residues of the herbicide bentazon (3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide) and its 6- and 8-hydroxy metabolites in or on the following food commodities:

Commodity	Parts per million
Bean, dry, seed	0.05
Bean, succulent	0.5
Corn, field, forage	3.0
Corn, field, grain	0.05
Corn, field, stover	3.0
Corn, pop, grain	0.05
Corn, sweet, kernel plus cob with husks removed	0.05
Cowpea, forage	10.0
Cowpea, hay	3.0
Flax, seed	1.0
Pea, dry, seed	1.0
Pea, field, hay	8.0
Pea, field, vines	3.0
Pea, succulent	3.0
Peanut	0.05
Peanut, hay	3.0
Pepper, nonbell	0.05
Peppermint, tops	1.0
Rice, grain	0.05
Rice, hulls	0.25
Sorghum, forage	0.20
Sorghum, grain, grain	0.05
Sorghum, grain, stover	0.05
Soybean, forage	8.0
Soybean, hay	8.0
Soybean, seed	0.05
Spearmint, tops	1.0

40 CFR 180.355(a)(1) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2017: https://www.ecfr.gov

Hazardous Substances Data Bank (HSDB)

Tolerances are established for the combined residues of the herbicide bentazon (3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide) and its metabolite 2-amino-N-isopropyl benzamide (AIBA) in or on the following food commodities:

Commodity	Parts per million
Cattle, fat	0.05
Cattle, meat byproducts	0.05
Cattle, meat	0.05
Egg	0.05
Goat, fat	0.05
Goat, meat byproducts	0.05
Goat, meat	0.05
Hog, fat	0.05
Hog, meat byproducts	0.05
Hog, meat	0.05
Milk	0.02
Poultry, fat	0.05
Poultry, meat byproducts	0.05
Poultry, meat	0.05
Sheep, fat	0.05
Sheep, meat byproducts	0.05
Sheep, meat	0.05

40 CFR 180.355(a)(2) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2017: https://www.ecfr.gov

Hazardous Substances Data Bank (HSDB)

Tolerances with regional registration as defined in section 180.1(m), are established for combined residues of the herbicide, bentazon (3-isopropyl-1H-2, 1,3-benzothiadiazin-4(3H)-one-2,2-dioxide) and its 6- and 8-hydroxy metabolites in or on the following food commodities:

Commodity	Parts per million
Clover, forage	1.0
Clover, hay	2.0

40 CFR 180.355(c) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2017: https://www.ecfr.gov

Hazardous Substances Data Bank (HSDB)

11.6.5 Personal Protective Equipment (PPE)

Eye/face protection: Face shield and safety glasses. Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Skin protection: Handle with gloves.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Body Protection: Complete suit protecting against chemicals. The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Respiratory protection: For nuisance exposures use type P95 (US) or type P1 (EU EN 143) particle respirator. For higher level protection use type OV/AG/P99 (US) or type ABEK-P2 (EU EN 143) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

Chemical-resistant apron when cleaning equipment, mixing, or loading. Chemical-resistant gloves. Protective eyewear. Protective clothing and boots when handling undiluted product.

Crop Protection Handbook Volume 100, Meister Media Worldwide, Willoughby, OH 2014, p. 130

Hazardous Substances Data Bank (HSDB)

11.6.6 Exposure Prevention

AVOID EXPOSURE OF ADOLESCENTS AND CHILDREN!

ILO International Chemical Safety Cards (ICSC)

11.6.7 Inhalation Prevention

Avoid inhalation of dust and mist. Use local exhaust or breathing protection.

ILO International Chemical Safety Cards (ICSC)

11.6.8 Skin Prevention

Protective gloves.

ILO International Chemical Safety Cards (ICSC)

11.6.9 Eye Prevention

Wear safety goggles.

ILO International Chemical Safety Cards (ICSC)

11.6.10 Ingestion Prevention

Do not eat, drink, or smoke during work. Wash hands before eating.

ILO International Chemical Safety Cards (ICSC)

11.7 Transport Information

11.7.1 Packaging and Labelling

Do not transport with food and feedstuffs.

ILO International Chemical Safety Cards (ICSC)

11.7.2 EC Classification

Symbol: Xn; R: 22-36; S: (2)-24-37-61

ILO International Chemical Safety Cards (ICSC)

11.8 Regulatory Information

11.8.1 Federal Drinking Water Guidelines

EPA 200 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

Hazardous Substances Data Bank (HSDB)

11.8.2 State Drinking Water Standards

(CA) CALIFORNIA 18 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

Hazardous Substances Data Bank (HSDB)

11.8.3 State Drinking Water Guidelines

(WI) WISCONSIN 300 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

Hazardous Substances Data Bank (HSDB)

11.8.4 FIFRA Requirements

Tolerances are established for the combined residues of the herbicide bentazon (3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide) and its 6- and 8-hydroxy metabolites in or on the following food commodities:

Commodity
Bean, dry, seed
Bean, succulent
Corn, field, forage
Corn, field, grain
Corn, field, stover
Corn, pop, grain
Corn, sweet, kernel plus cob with husks removed
Cowpea, forage
Cowpea, hay
Flax, seed
Pea, dry, seed
Pea, field, hay
Pea, field, vines
Pea, succulent
Peanut
Peanut, hay
Pepper, nonbell
Peppermint, tops
Rice, grain
Rice, hulls
Sorghum, forage
Sorghum, grain, grain
Sorghum, grain, stover
Soybean, forage
Soybean, hay
Soybean, seed
Spearmint, tops

*40 CFR 180.355(a)(1) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2017: **https://www.ecfr.gov***

Hazardous Substances Data Bank (HSDB)

Tolerances are established for the combined residues of the herbicide bentazon (3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide) and its metabolite **2-amino-N-isopropyl benzamide** (AIBA) in or on the following food commodities:

Commodity
Cattle, fat
Cattle, meat byproducts
Cattle, meat
Egg
Goat, fat
Goat, meat byproducts
Goat, meat
Hog, fat
Hog, meat byproducts

Commodity
Hog, meat
Milk
Poultry, fat
Poultry, meat byproducts
Poultry, meat
Sheep, fat
Sheep, meat byproducts
Sheep, meat

40 CFR 180.355(a)(2) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2017: https://www.ecfr.gov

Hazardous Substances Data Bank (HSDB)

Tolerances with regional registration as defined in section 180.1(m), are established for combined residues of the herbicide, bentazon (3-isopropyl-1H-2, 1,3-benzothiadiazin-4(3H)-one-2,2-dioxide) and its 6- and 8-hydroxy metabolites in or on the following food commodities:

Commodity
Clover, forage
Clover, hay

40 CFR 180.355(c) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2017: https://www.ecfr.gov

Hazardous Substances Data Bank (HSDB)

Based on the reviews of the generic data for the active ingredient bentazon, the Agency has sufficient information on the health effects of bentazon and on its potential for causing adverse effects in fish and wildlife and the environment. Therefore, the Agency concludes that products containing bentazon for all uses are eligible for reregistration. The Agency has determined that bentazon products, labeled and used as specified in this Reregistration Eligibility Decision, will not pose unreasonable risks or adverse effects to humans or the environment.

USEPA/Office of Prevention, Pesticides and Toxic Substances; Reregistration Eligibility Decision Document for Bentazon p.42 EPA 738-R-94-029 (September 1994). Available from, as of November 2, 2017: https://www.epa.gov/pesticides/reregistration/status.htm

Hazardous Substances Data Bank (HSDB)

As the federal pesticide law FIFRA directs, EPA is conducting a comprehensive review of older pesticides to consider their health and environmental effects and make decisions about their continued use. Under this pesticide reregistration program, EPA examines newer health and safety data for pesticide active ingredients initially registered before November 1, 1984, and determines whether the use of the pesticide does not pose unreasonable risk in accordance to newer safety standards, such as those described in the Food Quality Protection Act of 1996. Bentazon is found on List A, which contains most pesticides that are used on foods and, hence, have a high potential for human exposure. List A consists of the 194 chemical cases (or 350 individual active ingredients) for which EPA issued registration standards prior to FIFRA '88. Case No: 0182; Pesticide type: Herbicide; Registration Standard Date: 09/28/85; Case Status: RED Approved 09/94; OPP has made a decision that some/all uses of the pesticide are eligible for reregistration, as reflected in a Reregistration Eligibility Decision (RED) document.; Active ingredient (AI): Sodium bentazon; Data Call-in (DCI) Date(s): 08/29/90; AI Status: OPP has completed a Reregistration Eligibility Decision (RED) document for the case/AI.

United States Environmental Protection Agency/ Prevention, Pesticides and Toxic Substances; Status of Pesticides in Registration, Reregistration, and Special Review. (1998) EPA 738-R-98-002, p. 90

Hazardous Substances Data Bank (HSDB)

11.9 Other Safety Information

11.9.1 Toxic Combustion Products

Special hazards arising from the substance or mixture: Carbon oxides, nitrogen oxides (NOx), sulfur oxides.

Sigma-Aldrich; Safety Data Sheet for Bentazon. Product Number: 32052, Version 5.2 (Revision Date 07/02/2014). Available from, as of October 26, 2017: https://www.sigmaaldrich.com/safety-center.html

Hazardous Substances Data Bank (HSDB)

11.9.2 Special Reports

USEPA/Office of Prevention, Pesticides and Toxic Substances; Reregistration Eligibility Decision Document for Bentazon EPA 738-R-94-029 (September 1994). The RED summarizes the risk assessment conclusions and outlines any risk reduction measures necessary for the pesticide to continue to be registered in the USA.[Available from, as of October 26, 2017: http://www.epa.gov/pesticides/reregistration/status.htm]

Hazardous Substances Data Bank (HSDB)

WHO/IPCS; Pesticide Residues in Food - 1991. Part II - Toxicology (1992)

Hazardous Substances Data Bank (HSDB)

12 Toxicity

12.1 Toxicological Information

12.1.1 Toxicity Summary

IDENTIFICATION AND USE: Bentazone is a white, crystalline solid. It was formerly used as an herbicide. HUMAN STUDIES: Bentazone is irritating to eyes and mucous membranes. A 50-year-old male who had sprayed corn with a solution of bentazone was admitted to the hospital with sweating, fever, nausea, vomiting of aqueous and hemorrhagic content, and bloody, watery stools. He was treated according to the symptoms including extracorporeal hemodialysis, but eventually suffered from multiorgan failure (acute respiratory failure, acute liver failure, coagulopathy, acute renal failure, metabolic acidosis, and gastrointestinal bleeding) and died 11.35 hr after admittance. In another case, intentional poisoning with 130 g of bentazone resulted in vomiting, fever, sweating, pipe-like muscle rigidity, sinus tachycardia, drowsiness, leukocytosis, rhabdomyolysis and hepatorenal damage. ANIMAL STUDIES: Bentazone is not a skin irritant but was a moderate eye irritant in rabbits. It is a skin sensitizer in guinea-pigs. In a chronic toxicity study, bentazone was administered to rats (50 of each sex per group) via a diet at doses 0, 5, 17 and 76 mg/kg bw per day for 2 years. Statistical analysis of tumor incidence did not reveal any significance among the groups tested. Bentazone was not teratogenic in rabbits or rats. In rat developmental studies, it increased post-implantation loss, skeletal variations (incomplete or absent ossification in the phalangeal nuclei of the extremities, sternebrae and cervical vertebrae) and reduced body weights of fetuses surviving to day 21 at 250 mg/kg bw per day. Dietary administration of bentazone to rats at dose levels of 0, 300, 1000 and 3500 ppm did not result in any indication of neurotoxicity. In vitro genotoxicity studies included bacterial reverse mutation assays on Salmonella typhimurium and Escherichia coli, DNA damage and repair studies on E. coli and Saccharomyces cerevisiae, and chromosomal aberration and forward mutation assays in CHO cells. In vivo studies included chromosome analyses in mice and rats, unscheduled DNA synthesis tests in mice, and mutation assays in germ cells for mice and rats. Bentazone gave negative results in all of these studies. ECOTOXICITY STUDIES: Bentazone affected zebrafish embryos and associated bacterial communities. It was nontoxic to bees.

Hazardous Substances Data Bank (HSDB)

12.1.2 NIOSH Toxicity Data

The National Institute for Occupational Safety and Health (NIOSH)

12.1.3 Evidence for Carcinogenicity

WEIGHT OF EVIDENCE CHARACTERIZATION: Under EPA's 1986 Guidelines for Carcinogen Risk Assessment, Bentazon would be classified as evidence of non-carcinogenicity for humans, or a Group E chemical. Under EPA's proposed guidelines for carcinogen risk assessment, Bentazon would be characterized as not likely to be carcinogenic to humans by any route of exposure. Additionally, the Health Effects Division, Office of Pesticide Programs cancer peer review committee has concluded after evaluating the known and submitted studies that the animal bioassays were essentially negative for a carcinogenic effect from chronic feeding, and under the older classification system the chemical was classed as an E for carcinogenic potential. The metabolic pathways of Bentazon and the handling of it by the mammalian system are well understood and do not produce any significant suspect reactive species. The mutagenicity studies do not indicate a mutagenicity hazard from the chemical and structure-activity comparisons to similar chemical structures are negative for significant effects regarding carcinogenic potential. HUMAN CARCINOGENICITY DATA: The Agency is unaware of any data available for review. ANIMAL CARCINOGENICITY DATA: Studies were considered adequate for evaluation of the carcinogenic potential in animals. The results were considered to not be indicative of a hazard to test animals. ...

U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS). Summary on Bentazon (25057-89-0). Available from, as of October 26, 2017: ***https://www.epa.gov/iris/***

Hazardous Substances Data Bank (HSDB)

12.1.4 Carcinogen Classification

Carcinogen Classification	No indication of carcinogenicity to humans (not listed by IARC).

Toxin and Toxin Target Database (T3DB)

12.1.5 Exposure Routes

The substance can be absorbed into the body by inhalation and by ingestion.

ILO International Chemical Safety Cards (ICSC)

12.1.6 Eye Symptoms

Redness. Pain.

- ILO International Chemical Safety Cards (ICSC)

12.1.7 Adverse Effects

Skin Sensitizer - An agent that can induce an allergic reaction in the skin.

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

12.1.8 Acute Effects

- ChemIDplus

12.1.9 Toxicity Data

LC50 (rat) = 5,100 mg/m3/4h

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

12.1.10 Interactions

Maize black Mexican sweet cell suspension cultures were used to study the effects of various cytochrome p450 monooxygenase inhibitors on the uptake and metabolism of the herbicide bentazon. Maize cells rapidly absorbed bentazon and metabolized it via aryl hydroxylation and glycosylation to a glycosyl conjugate of **6-hydroxybentazon**. Maize black Mexican sweet cells accumulated bentazon to levels approximately 20 fold greater than those in the external medium. When maize black Mexican sweet cells were incubated in an external medium containing 25 uM bentazon, the formation of the glycosyl conjugate (ca 2 nmol/min/g fresh wt) was rate limited by aryl hydroxylation. **Tetcyclacis**, a plant growth retardant, **phenylhydrazine**, a mechanism based cytochrome p450 inhibitor, and **piperonyl butoxide**, an insecticide synergist, inhibited bentazon metabolism with I50 values of approximately 0.1, 1.0, and 1.0 uM, respectively. Other mechanism based cytochrome p450 inhibitors, **3(2,4-dichlorophenoxy)-1-propyne** and **aminobenzotriazole**, also inhibited bentazon metabolism but were less effective. The results obtained with selected inhibitors are consistent with the hypothesis that aryl hydroxylation of bentazon is catalyzed by a cytochrome p450 monooxygenase.

Gronwald JW, Connelly JA; Pestic Biochem Physiol 40 (3): 284-94 (1991)

- Hazardous Substances Data Bank (HSDB)

12.1.11 Antidote and Emergency Treatment

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing **water**. Do not induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

- Hazardous Substances Data Bank (HSDB)

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer **oxygen** by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with **water**. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of **water** for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

Hazardous Substances Data Bank (HSDB)

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag valve mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta agonist such as albuterol for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W TKO /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with diazepam or lorazepam ... . Use proparacaine hydrochloride to assist eye irrigation ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160-1

Hazardous Substances Data Bank (HSDB)

Decontaminate skin promptly by washing with soap and water. Treat contamination of the eyes immediately by prolonged flushing with copious amounts of clean water. If dermal or ocular irritation persists, medical attention should be obtained without delay. /Other herbicides/

U.S. Environmental Protection Agency/Office of Prevention, Pesticides, and Toxic Substances. Roberts, J.R., Reigart, J.R. Recognition and Management of Pesticide Poisonings. 6th ed. 2013. EPA Document No. EPA 735K13001, and available in electronic format at: https://www2.epa.gov/pesticide-worker-safety, p. 125

Hazardous Substances Data Bank (HSDB)

For more Antidote and Emergency Treatment (Complete) data for Bentazon (7 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.1.12 Human Toxicity Excerpts

/SIGNS AND SYMPTOMS/ Irritating to eyes and mucous membranes.

Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-340

Hazardous Substances Data Bank (HSDB)

/CASE REPORTS/ This study presents two cases of lethal bentazone poisonings, their clinical presentation, the course of the disease and the autopsy findings. The first is a 50-year-old male who had sprayed corn with a solution of bentazone and was admitted to the hospital with sweating, fever, nausea, vomiting of aqueous and hemorrhagic content, and bloody, watery stools. He was treated according to the symptoms including extracorporeal hemodialysis, but eventually suffered from multiorgan failure (acute respiratory failure, acute liver failure, coagulopathy, acute renal failure, metabolic acidosis, and gastrointestinal bleeding) and died 11.35 hr after admittance. The cause of death was probable bentazone intoxication. The second case, also a male, aged 49 who committed suicide by ingesting a bentazone solution. He was transferred to the hospital prostrated and cyanotic and died 14.15 hr after admittance despite all efforts by the hospital staff. The cause of death was acute bentazone intoxication.

PMID:28407445

Skavic P et al; J Forensic Sci doi: 10.1111/1556-4029.13518. (Epub ahead of print) (2017)

Hazardous Substances Data Bank (HSDB)

/CASE REPORTS/ A 27-year-old robust man, without any medical or surgical history, attempted to commit suicide by consuming 300 mL Basagran (about 130 g bentazone). This poisoning resulted in vomiting, fever, sweating, pipe-like muscle rigidity, sinus tachycardia, drowsiness, leukocytosis, rhabdomyolysis and hepatorenal damage. Empirical treatment with bromocriptine was temporally associated with resolution of the above signs and symptoms. His clinical presentations and the effect of bromocriptine may be indicative that Basagran poisoning mimicks neuroleptic malignant syndrome.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.86 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

/CASE REPORTS/ A case of fatal suicidal bentazone poisoning was presented along with a description of the different analytical methods involved. A 56-year-old farmer was examined by the family doctor 1 hour after voluntarily ingesting 500 mL of FIGHTER (about 250 g bentazone). He presented a Glasgow score of 15, polypnea, diarrhea and vomiting. During transport by ambulance to the hospital, he tossed, sweated and suddenly presented breathing difficulty followed by heart failure. The patient died within 2 hours post-ingestion. Blood and urine samples were taken just before death. Bentazone plasma and urine levels were 1500 and 1000 mg/L, respectively.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.86 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

For more Human Toxicity Excerpts (Complete) data for Bentazon (9 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.1.13 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Acute Exposure/ Acute oral toxicity studies are available for a number of species (i.e. rat, guinea pig, cat, dog and rabbit). ... No significant differences in LD50 were found between the free acid and the sodium salt. Signs of toxicity included dyspnoea, apathy, cachexia, staggering and poor general state. ... Bentazone is not a skin irritant but was a moderate eye irritant in rabbits. It is a skin sensitizer in guinea-pigs.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.38 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Bentazone (batch N 194, purity 97.64%) was administered dermally to SPF New Zealand White rabbits (five of each sex per dose) for 21 consecutive days at a dose of 0 (solvent control), 250, 500 or 1000 mg/kg bw per day. The test material was applied for 6 hours/day as 0.5% aqueous Tylose CB 30.000 solution (cleaned sodium carboxymethylcellulose in distilled water) under semi-occlusive dressing covering at least 10% of the body surface. The animals were housed singly under controlled conditions, and each received a daily ration of about 130 g of standardized diet. A daily ration of approximately 250 mL/animal was available as drinking-water. The test substance preparations were made up each workday immediately before application. Clinical observations were made twice daily. A check for skin findings was carried out daily about 30 minutes after removal of the dressing. Feed consumption and body weight were recorded weekly. Clinico-chemical, hematological (including clotting analysis for thromboplastin time), gross pathological and histopathological examinations were carried out at the end of the study. There were no deaths during the study period. No clinical signs of systemic toxicity were observed. No treatment-related differences in feed consumption were noted during the study. Body weight in test animals was comparable with that seen in controls. No signs of irritation on the treated skin could be observed in all animals of the test groups. The treated skin of these animals was discolored (yellow) by the test substance. Adhesive tape caused mechanical skin lesions beside the treated area. Hemorrhagic round areas with sharp margins and crateriform retractions were observed on the clipped dorsal area of all animals used as controls (solvent control). No treatment-related effects on clinical chemistry or hematology values were apparent in males or females. No pathomorphological findings considered to be treatment related were

diagnosed. No treatment-related significantly different mean absolute or relative weight parameters and no treatment-related gross lesions or microscopic findings were detected. No treatment-related skin changes were detected. The NO AEL for dermal toxicity (local and systemic) of bentazone was greater than 1000 mg/kg bw.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.49-50 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ ... Bentazone (purity 97.8%) was applied daily for 6 hours to the clipped intact dorsal skin of New Zealand White rabbits (mean weight 2.29 kg for males and 2.27 kg for females; five of each sex per dose) over a period of 3 weeks using a semi-occlusive dressing. The doses were 250, 500 and 1000 mg/kg bw per day. A control group (five of each sex) was treated with solvent (0.5% aqueous carboxymethylcellulose). Feed consumption was determined once a week over the course of 1 day. Body weight was determined weekly. The animals were carefully inspected twice daily (before and after exposure). Skin findings were recorded daily (about 30-60 minutes after removal of the dressing). At the end of the study, clinicochemical and hematological examinations were carried out. All animals were assessed by gross pathology. Subsequently, a histopathological examination was carried out. After a thorough assessment (clinical examination, clinical chemistry, hematology and pathology), the dermal application of bentazone did not lead to any substance-related findings at the doses tested. Some changes were attributed to an infection by coccidia. The NOAEL was greater than 1000 mg/kg bw per day for both sexes of rabbits.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.49 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ The 21-day dermal toxicity of bentazone technical (purity not given) was tested in New Zealand White rabbits (weight between 2.3 and 3.1 kg) with dermal doses of the test substance of 0, 250, 500 or 1000 mg/kg bw applied daily for a period of 8 hours to the intact and scarified skin of six animals of each sex per dose for a period of 21 days. The control animals were treated in the same way with tylose at a dose of 2 mL/kg bw. The animals with intact skin (i.e. half of the total) were kept under observation for a further 21 days after termination of treatment. Behavior and feed and water consumption were checked daily. Body weights were determined weekly. Clinical, clinicochemical, hematological, gross pathological and histopathological examinations as well as urine analysis were carried out. Very slight, transient erythema was detected on the intact and scarified skin, the latter being slightly more affected. However, in no case did the reactions exceed those of the control animals. More extensive skin injuries, such as edema and necrosis, were not observed. The test and control animals showed no differences during the withdrawal period. Behavior, condition of coat, feed and water consumption, body weight gain, hematological and biochemical tests, urine analysis, gross pathological findings and organ weights at necropsy after 3 or 6 weeks of testing were similar for treated and control animals. Histological investigations carried out after 3 weeks on the animals with scarified skin and after a further 3 weeks' observation on the animals with intact skin revealed in isolated cases negligible inflammatory infiltration on the application site and on the untreated skin. No significant differences could be observed between the treated animals and the control animals. The isolated and very slight findings in other organs can be classified as spontaneous pathology. The NO AEL for dermal toxicity was above 1000 mg/kg bw per day for male and female animals.

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.49 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

For more Non-Human Toxicity Excerpts (Complete) data for Bentazon (25 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.1.14 Non-Human Toxicity Values

LD50 Rat oral 850-2470 mg/kg bw /Includes free acid and sodium salt forms; From table/

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.39 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

LD50 Guinea pig oral 1100 mg/kg bw /Free acid and sodium salt forms; From table/

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.39 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

LD50 Rabbit oral 1139 mg/kg bw /From table/

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.39 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

LD50 Rat dermal >5000 mg/kg bw /Acid form; From table/

WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food - 2012, Toxicological Evaluations p.39 (2012). Available from, as of October 27, 2017: https://www.who.int/foodsafety/publications/jmpr-monographs/en/

Hazardous Substances Data Bank (HSDB)

For more Non-Human Toxicity Values (Complete) data for Bentazon (26 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.1.15 Ecotoxicity Values

LC50; Species: Colinus virginianus (Northern Bobwhite Quail) juvenile; dietary >10000 ppm for 8 days /42% purity/

USEPA/OPP; Pesticide Ecotoxicity Database (1992) as cited in the ECOTOX database. Available from, as of October 16, 2017

Hazardous Substances Data Bank (HSDB)

LC50; Species: Eisenia fetida (Earthworm) adult, sexually mature; dermal, filter paper 3.27 kg/ha for 48 hr (95% confidence interval: 2.50-4.28 kg/ha)

Pizl V; Pedobiologia 32 (3/4): 227-232 (1988) as cited in the ECOTOX database. Available from, as of October 16, 2017

Hazardous Substances Data Bank (HSDB)

EC50; Species: Nostoc muscorum (Blue-Green Algae) Axenic clonal stock; Conditions: freshwater, static, 28 °C; Concentration: 1 mM for 72 hr; Effect: physiology, decreased photosynthesis

Galhano V et al; Environ Toxicol 25 (2): 147-156 (2010) as cited in the ECOTOX database. Available from, as of October 17, 2017

Hazardous Substances Data Bank (HSDB)

EC50; Species: Nostoc muscorum (Blue-Green Algae) Axenic clonal stock; Conditions: freshwater, static, 28 °C; Concentration: 6.8 mM for 72 hr; Effect: biochemistry, decreased phycobiliproteins

Galhano V et al; Environ Toxicol 25 (2): 147-156 (2010) as cited in the ECOTOX database. Available from, as of October 17, 2017

Hazardous Substances Data Bank (HSDB)

For more Ecotoxicity Values (Complete) data for Bentazon (23 total), please visit the **HSDB record page**.

Hazardous Substances Data Bank (HSDB)

12.1.16 Ecotoxicity Excerpts

/AQUATIC SPECIES/ This study aimed to assess the effects of Basagran on zebrafish (Danio rerio) embryos. The embryos were exposed to Basagran at concentrations ranging from 120.0 to 480.6 mg/L, and the effects on embryo development (up to 96 hr) and bacterial communities of 96 hr-larvae were assessed. The embryo development response was time-dependent and concentration-dependent (106.35 < EC50 < 421.58 mg/L). The sensitivity of embryo-related endpoints decreased as follows: blood clotting in the head and/or around the yolk sac > delay or anomaly in yolk sac absorption > change in swimming equilibrium > development of pericardial and/or yolk sac edema > scoliosis. A PCR-DGGE analysis was used to evaluate changes in the structure, richness, evenness and diversity of bacterial communities after herbicide exposure. A herbicide-induced structural adjustment of bacterial community was observed. In this study, it was successfully demonstrated that Basagran affected zebrafish embryos and associated bacterial communities, showing time-dependent and concentration-dependent embryos' developmental response and structural changes in bacterial community. Thus, this work provides for the first time a complementary approach, which is useful to derive robust toxicity thresholds considering the embryo-microbiota system as a whole. The aquatic hazard assessment will be strengthened by combining current ecotoxicological tests with molecular microbiology tools.

PMID:27913070

Oliveira JM et al; Environ Pollut 221: 52-63 (2017)

Hazardous Substances Data Bank (HSDB)

/OTHER TERRESTRIAL SPECIES/ /Nontoxic to bees./

Crop Protection Handbook Volume 100, Meister Media Worldwide, Willoughby, OH 2014, p. 130

Hazardous Substances Data Bank (HSDB)

/OTHER TOXICITY INFORMATION/ The toxicological effects of the active ingredients of the herbicides **diuron** and bentazon on the activity of acetylcholinesterase (AChE) of krait (Bungarus sindanus) venom and electric eel (Electrophorus electricus) were studied. The **diuron** and bentazon caused non-competitive inhibition of AChE from both species. For the venom AChE, the calculated IC50 for **diuron** and bentazon were found to be 3.25 and 0.14 uM, while for eel AChE, the respective IC50 values were 3.6 and 0.135 uM. In comparison, bentazon was a more potent inhibitor than **diuron** of AChE from both species. The insecticide **lindane** did not have any inhibitory effect on AChE activity in either species, even when tested at high concentrations (200-800 uM).

PMID:22653306

Ahmed M et al; Bull Environ Contam Toxicol 89 (2): 229-33 (2012)

Hazardous Substances Data Bank (HSDB)

12.1.17 Ongoing Test Status

EPA has released the Interactive Chemical Safety for Sustainability (iCSS) Dashboard. The iCSS Dashboard provides an interactive tool to explore rapid, automated (or in vitro high-throughput) chemical screening data generated by the Toxicity Forecaster (ToxCast) project and the federal Toxicity Testing in the 21st century (Tox21) collaboration. /The title compound was tested by ToxCast and/or Tox21 assays/[USEPA; ICSS Dashboard Application; Available from, as of November 16, 2017: http://actor.epa.gov/dashboard/]

Hazardous Substances Data Bank (HSDB)

12.2 Ecological Information

12.2.1 EPA Ecotoxicity

Pesticide Ecotoxicity Data from EPA

EPA Pesticide Ecotoxicity Database

12.2.2 US EPA Regional Screening Levels for Chemical Contaminants

Resident Soil (mg/kg)	1.90e+02
Industrial Soil (mg/kg)	2.50e+03
Tapwater (ug/L)	5.70e+01
Risk-based SSL (mg/kg)	1.20e-02
Chronic Oral Reference Dose (mg/kg-day)	3.00e-02
Fraction of Contaminant Absorbed in Gastrointestinal Tract	1
Fraction of Contaminant Absorbed Dermally from Soil	0.1

EPA Regional Screening Levels for Chemical Contaminants at Superfund Sites

12.2.3 US EPA Regional Removal Management Levels for Chemical Contaminants

Resident Soil (mg/kg)	1.90e+03
Industrial Soil (mg/kg)	2.50e+04
Tapwater (ug/L)	5.70e+02
Chronic Oral Reference Dose (mg/kg-day)	3.00e-02
Fraction of Contaminant Absorbed in Gastrointestinal Tract	1
Fraction of Contaminant Absorbed Dermally from Soil	0.1

EPA Regional Screening Levels for Chemical Contaminants at Superfund Sites

12.2.4 ICSC Environmental Data

Avoid release to the environment in circumstances different to normal use.

ILO International Chemical Safety Cards (ICSC)

12.2.5 Environmental Fate/Exposure Summary

Bentazon's production may result in its release to the environment through various waste streams; its use as an herbicide will result in its direct release to the environment. If released to air, a vapor pressure of 4.05X10-8 mm Hg at 20 °C indicates bentazon will exist solely in the particulate phase in the atmosphere. Particulate-phase bentazon will be removed from the atmosphere by wet or dry deposition. Bentazon absorbs light at wavelengths >290 nm and, therefore, is expected to be susceptible to direct photolysis by sunlight. If released to soil, bentazon is expected to have very high to high mobility based upon experimental Koc values ranging from 0 to 46. The pKa of bentazon is 3.3, indicating that this compound will exist almost entirely in the anion form in the environment and anions generally do not adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts. Volatilization from moist soil is not expected because the compound exists as an anion and anions do not volatilize. Bentazon is not expected to volatilize from dry soil surfaces based upon its vapor pressure. In aerobic soils, reported degradation half-lives of 6.7 to 50 days suggest that under certain conditions biodegradation may be an important environmental fate process in soil. If released into water, bentazon is not expected to adsorb to suspended solids and sediment based upon the Koc values. Bentazon was not degraded in biodegradation experiments anaerobic aquifer conditions but the available soil studies would suggest that biodegradation may be an important environmental fate process in water. A pKa of 3.3 indicates bentazon will exist almost entirely in the anion form at pH values of 5 to 9 and, therefore, volatilization from water surfaces is not expected to be an important fate process. A BCF of 3.7 suggests the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since bentazon was stable to hydrolysis in pH 5, 7, and 9 buffer solutions. Occupational exposure to bentazon may occur through inhalation of dust and dermal contact with this compound at workplaces where bentazon is produced or used. Limited monitoring and use data indicate that the general population may be exposed to bentazon via ingestion of contaminated water. (SRC)

Hazardous Substances Data Bank (HSDB)

12.2.6 Artificial Pollution Sources

Bentazon's production may result in its release to the environment through various waste streams; its use as an herbicide(1) will result in its direct release to the environment(SRC).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

Hazardous Substances Data Bank (HSDB)

12.2.7 Environmental Fate

TERRESTRIAL FATE: Based on a classification scheme(1), a Koc range of 0 to 46(2,3) indicates that bentazon is expected to have very high to high mobility in soil(SRC). The pKa of bentazon is 3.3(4), indicating that this compound will exist almost entirely in anion form in the environment and anions generally do not adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts(5). Volatilization from moist soil is not expected because the compound exists as an anion and anions do not volatilize. Bentazon is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 4.05X10-8 mm Hg at 20 °C(2). In aerobic soils, reported degradation half-lives of 6.7 to 50 days(2,6) suggests that under certain conditions biodegradation may be an important environmental fate process in soil(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010) (3) Kenaga EE; Ecotoxicology and Environmental Safety 4: 26-8 (1980) (4) O'Neil MJ, ed; The Merck Index. 15th ed. Cambridge, UK: The Royal Society of Chemistry. p. 185 (2013) (5) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds. Boca Raton, FL: Lewis Publ (2000) (6) Wagner SC et al; J Agric Food Chem 44: 1593-8 (1996)

Hazardous Substances Data Bank (HSDB)

FIELD STUDY: Field dissipation studies were conducted in Texas on sandy soil (0.5% OM) planted with peanuts, Mississippi on a Commerce silt loam soil planted with soybeans and peanuts, Mississippi on a Sharkey silty clay loam soil planted with soybeans, North Carolina on acidic, sandy loam soil (2.8% OM) planted to peanuts, Minnesota on clay soil planted to soybeans, and Idaho on a sandy loam soil. Bentazon, applied as a wettable powder or soluble concentrate at cumulative rates of 1.0 to 10 lbs a.i./A, had field dissipation half-lives of 7 to 33 days. The degradate AIBA was detected (< 0.05 ppm) in the North Carolina, Mississippi, Alabama, and Idaho field dissipation studies. Bentazon and 2-amino-N-isopropylbenazamide were not detected in deep soil samples (> 12 inches of soil) in field studies.

(1) USEPA/OPP; Reregistration Eligibility Decisions (REDs) Database. Bentazone. EPA 738-R-94-029. Available from, as of Nov 20, 2017: https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1

Hazardous Substances Data Bank (HSDB)

AQUATIC FATE: Based on a classification scheme(1), a Koc range of 0 to 46(2,3) indicates that bentazon is not expected to adsorb to suspended solids and sediment(SRC). A pKa of 3.3(4) indicates bentazon will exist almost entirely in the anion form at pH values of 5 to 9 and, therefore, volatilization from water surfaces is not expected to be an important fate process(SRC). According to a classification scheme(5), a whole body BCF of 3.7 in bluegill sunfish(6), suggests the potential for bioconcentration in aquatic organisms is low(SRC). Complete photolysis of bentazon took place within 16 hours in distilled water at pH 6.8 when irradiated with UV light(7,8). Bentazon was not degraded in biodegradation experiments anaerobic aquifer conditions(9) but the available soil studies would suggest that biodegradation may an important environmental fate process in water.(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010) (3) Kenaga EE; Ecotoxicology and Environmental Safety 4: 26-8 (1980) (4) O'Neil MJ, ed; The Merck Index. 15th ed. Cambridge, UK: The Royal Society of Chemistry. p. 185 (2013) (5) Franke C et al; Chemosphere 29: 1501-14 (1994) (6) Jackson SH et al; J Agric Food Chem 57: 958-67 (2009) (7) Chiron S et al; Environ Toxicol Chem 14: 1287-98 (1995) (8) Harrison SK, Wax LM; Weed Sci 34: 81-7 (1986) (9) Albrechtsen H-J, et al; Pest Manag Sci 57: 341-50 (2001)

Hazardous Substances Data Bank (HSDB)

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), bentazon, which has a vapor pressure of 4.05X10-8 mm Hg at 20 °C(2), is expected to exist solely in the particulate phase in the ambient atmosphere. Particulate-phase bentazon may be removed from the air by wet and dry deposition(SRC). Bentazon absorbs light at wavelengths between 330 and 335 nm(3) and, therefore, may be susceptible to direct photolysis by sunlight, since sunlight consists of wavelengths above 290 nm(SRC).

(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010) (3) Huber R, Otto S; Rev Environ Contam Toxicol 137: 111-34 (1994)

Hazardous Substances Data Bank (HSDB)

12.2.8 Environmental Biodegradation

AEROBIC: Bentazon can be rapidly utilized by bacteria and fungi(1). Bentazon was degraded in 8 soils with half-lives ranging from 6.7 to 15 days, and 38 to 50 days, for soils with and without a history of bentazon application, respectively(2), which suggests acclimation(SRC). In aerobic soil incubation experiments, approximately 80% of the initial bentazon applied remained after 28 days in sandy clay loam soil, in clay soil there was no significant conversion of bentazon after 30 days incubation(3). Rapid degradation in soil proceeds via the formation of short-lived hydroxy compounds which rapidly undergo further degradation(4). Bentazon has low soil persistence based on dissipation half-lives of 11-14 days in freshly collected field soils at 20 °C under aerobic conditions(4,5). In laboratory degradation studies, with soils of proven biological activity, a DT50 (average) of 17.8 days was reported; DT50 (field, average) was approximately 12 days; corresponding DT90 was 44 days(4). The average half-life of bentazon in laboratory soils was about 46 days(5).

(1) Humburg NE; Herbicide Handbook of the Weed Science Society of America. 6th ed. Champaign, IL: Weed Sci Soc Amer (1989) (2) Wagner SC et al; J Agric Food Chem 44: 1593-8 (1996) (3) Romero E et al; Pesticide Sci 47: 7-15 (1996) (4) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010) (5) Huber R, Otto S; Rev Environ Contam Toxicol 137: 111-34 (1994)

Hazardous Substances Data Bank (HSDB)

AEROBIC: Phenyl-ring labeled bentazon, degraded in mineral soils with a half-life of 24 days in clay loam soil, 31 days in loamy sand soil, and 65 days in sandy loam soil; methanol extractable residues in soil were bentazon, N-methyl-bentazon, and 8-chloro-bentazon. Ring-labeled bentazon had a half-life of 6 weeks in Sandhofen (German) loamy sand soil. Ring-labeled bentazon had half-lives ranging from < 2 weeks to 14 weeks in Limburgerhoff (German) loamy sand soil, Bruchfeld (German) sandy clay loam soil, Niedereschbach (German) loam soil, and Sandhofen (German) loamy sand soil; most of the methanol extractable bentazon residues (95%) were found in nonextractable soil fractions (or unavailable) over a 350 day incubation period; the degradate 2-amino-N-isopropylbenazamide was detected at low concentrations (<0.1 ppm)(1).

(1) USEPA/OPP; Reregistration Eligibility Decisions (REDs) Database. Bentazone. EPA 738-R-94-029. Available from, as of Nov 20, 2017: https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1

Hazardous Substances Data Bank (HSDB)

AEROBIC: Bentazon was not degraded in degradation experiments assessing aquifer degradation under aerobic conditions(1). Binding mechanism studies found that bentazon mixed with catechol in the presence of a laccase from the fungus Polyporus pinsitus was completely transformed in 30 minutes at pH 4.0. Results also showed that the transformation of bentazon decreases with increasing pH, but complete transformations of bentazon in high pH environments can still be achieved by increasing the concentration of catechol(2).

(1) Albrechtsen H-J, et al; Pest Manag Sci 57: 341-50 (2001) (2) Kim JE et al; Environ Sci Technol 31: 2392-2398 (1997)

Hazardous Substances Data Bank (HSDB)

ANAEROBIC: Phenyl-labeled bentazon, in flooded sandy loam soil and rice clay soil, did not degrade under anaerobic conditions(1). Bentazon was not degraded in degradation experiments assessing aquifer degradation under anaerobic conditions(2).

(1) USEPA/OPP; Reregistration Eligibility Decisions (REDs) Database. Bentazone. EPA 738-R-94-029. Available from, as of Nov 20, 2017: https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1 (2) Albrechtsen H-J, et al; Pest Manag Sci 57:341-50 (2001)

Hazardous Substances Data Bank (HSDB)

12.2.9 Environmental Abiotic Degradation

Based on its vapor pressure of 4.05X10-8 at 20 °C(1), bentazon is expected to exist solely in the particulate phase in the ambient atmosphere. Particulate-phase bentazon will be removed from the air by wet and dry deposition. Bentazon is not expected to undergo hydrolysis in the environment; bentazon was stable to hydrolysis in pH 5, 7, and 9 buffer solutions(2). Bentazon absorbs light at wavelengths between 330 and 335 nm(3) and, therefore, is expected to be susceptible to direct photolysis by sunlight, since sunlight consists of wavelengths above 290 nm(SRC). Bentazon undergoes rapid degradation in sunlight, ultimately to CO_2(1). Photodegration half-lives in soil and water have been measured as 63 hours and 941 hours, respectively(2).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010) (2) USEPA/OPP; Reregistration Eligibility Decisions (REDs) Database. Bentazone. EPA 738-R-94-029. Available from, as of Nov 20, 2017: https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1 (3) Huber R, Otto S; Rev Environ Contam Toxicol 137: 111-34 (1994)

Hazardous Substances Data Bank (HSDB)

12.2.10 Environmental Bioconcentration

Following an EPA guideline study, a whole body BCF of 3.7 was reported for bentazon in bluegill fish (Lepomic macrochirus) exposed for 28 days(1). According to a classification scheme(2), this BCF suggests the potential for bioconcentration in aquatic organisms is low(SRC). The BCF for 14C-bentazon residues in bluegill sunfish was 0.4 in edible fish tissue, 2.3 in non-edible fish tissues, and 1.4 in the whole body. In channel catfish, the maximum concentration of 14C-bentazon residues was 11.39 ug/g in non-edible tissues, 8.84 ug/g in whole tissues, and 2.47 ug/g in edible tissues(3).

(1) Jackson SH et al; J Agric Food Chem 57: 958-67 (2009) (2) Franke C et al; Chemosphere 29: 1501-14 (1994) (3) USEPA/OPP; Reregistration Eligibility Decisions (REDs) Database. Bentazone. EPA 738-R-94-029. Available from, as of Nov 20, 2017: https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1

Hazardous Substances Data Bank (HSDB)

12.2.11 Soil Adsorption/Mobility

The Koc of bentazon is reported as 13.3-176 mL/g with an average of 42 mL/g(1). Experimental soil adsorption coefficients of 0(2) and 33(3) have been reported. According to a classification scheme(4), these Koc values suggest that bentazon is expected to have very high to high mobility in soil. The pKa of bentazon is 3.3(5), indicating that this compound will exist almost entirely in anion form in the environment and anions generally do not adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts(6). It has been reported that, when used according to good agricultural practice, bentazone is degraded more quickly than it can leach; in lysimeter studies, average annual leachates contained <0.1 ug/L(1). Batch equilibrium studies, using conventional-till Dundee silt loam soil, with an organic carbon content of 0.64 and a pH of 5.77, reveal limited sorption of bentazon(7). Bentazon sorption was not affected by small differences in soil organic matter(7). Bentazon was poorly adsorbed in ten soils from Spain(8). A Pesticide Leaching Potential(PLP) Index of 50 for foliar application was calculated for bentazon using commonly reported Koc, persistence (half-life), and rate of application values(9,10). PLP values of 0 and 100 indicate no leaching potential and maximum leaching potential, respectively(9).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010) (2) Kenaga EE; Ecotoxic Environ Safety 4: 26-8 (1980). Available from, as of Nov 21, 2017: https://www.ncbi.nlm.nih.gov/pubmed/7379718 (3) Schuurmann G et al; Enviro Sci Tech 40:7005-7011 (2006)(4) Swann RL et al; Res Rev 85: 17-28 (1983) (5) O'Neil MJ, ed; The Merck Index. 15th ed. Cambridge, UK: The Royal Society of Chemistry. p. 185 (2013) (6) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds. Boca Raton, FL: Lewis Publ (2000) (7) Gaston LA et al; J Environ Qual 25: 120-6 (1996) (8) Romero E et al; Pesticide Sci 47: 7-15 (1996) (9) Warren RL, Weber JB; Soil Sci Soc North Carolina Proc 37: 23-35 (1994) (10) Weber JB; Soil Facts: Protecting Groundwater in North Carolina - A Pesticide and Soil Ranking System, North Carolina Cooperative Extension Service, NC, State Univ College of Agric and Life Sciences (1994)

Hazardous Substances Data Bank (HSDB)

Based on Kd values of 0.176 to 3.056, binding affinity to soil expected to be low. Bentazon may be expected to leach into ground and enter runoff to surface waters. Bentazon degradates N-methyl-bentazon and 8-chlorobentazon are relatively immobile in soil. The degradate 2-amino-N-isopropylbenazamide (AIBA) is mobile and nonpersistent in soil. Terrestrial field studies indicate bentazon dissipates rapidly in soils with reported half-lives of < 33 days under typical use conditions and leaching did not appear to be a major route of dissipation(1).

(1) USEPA/OPP; Reregistration Eligibility Decisions (REDs) Database. Bentazone. EPA 738-R-94-029. Available from, as of Nov 20, 2017: https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1

Hazardous Substances Data Bank (HSDB)

12.2.12 Volatilization from Water/Soil

A pKa of 3.3(1) indicates bentazon will exist almost entirely in the anion form at pH values of 5 to 9 and, therefore, volatilization from water surfaces is not expected to be an important fate process. Bentazon is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 4.05X10-8 mm Hg(2).

(1) O'Neil MJ, ed; The Merck Index. 15th ed. Cambridge, UK: The Royal Society of Chemistry. p. 185 (2013) (2) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Bentazone (25057-89-0) (2008-2010)

Hazardous Substances Data Bank (HSDB)

12.2.13 Environmental Water Concentrations

GROUND WATER: A pesticide detection study conducted in the Arkansas Delta analyzed groundwater samples collected from 77 irrigation wells between July 29 and September 23, 1996(1). Bentazon was the most frequently detected pesticide, accounting for 37% of total detections, with concentrations ranging from 0.0144 to 0.1153 ug/L. In a study seeking to characterize potential pesticide contamination of groundwater in eastern Arkansas, 231 wells located within 14 counties were sampled(2). Of the 231 wells sampled, only 17 had detectable pesticide concentrations. Bentazon was the most commonly detected pesticide occurring in 11 of the 17 contaminated wells with a concentration range of 0.2 to 152.1 ug/L. Bentazon was detected in 26 upper groundwater (below 3 meters) samples in the Netherlands at an average concentration of 0.2 ug/L(3). Bentazon has been detected in groundwater (maximum concentration in ug/L) in Germany(0.04), Italy(40), and in the Netherlands(1.1)(4). In a review of published Italian water monitoring papers from 1997 to 2013, bentazon was identified as one of the most detected herbicides in Italian ground waters with a maximum concentration of 16000 ng/L(5).

(1) Kresse T et al; Water Res Eng 2: 1206-1211 (1998) (2) Scott HD et al; Water Res Eng 2: 1200-1205 (1998) (3) Leistra M, Boesten JJTI; Agr Ecosyst Environ 26: 369-89 (1989) (4) Vandenberg R, Vanderlinden TMA; pp. 293-313 in Environ Sci Pollut Control Ser 11 (Groundwater Contam and Control). New York, NY: Marcel Dekker (1994) (5) Meffe R, Bustamanta I; Sci Tot Enviro 481: 280-295 (2014)

Hazardous Substances Data Bank (HSDB)

GROUND WATER: Bentazon has been detected at concentrations ranging from 0.01 to 120 parts per billion (ppb) in 11% (83 out of 750) of wells sampled from California, with the greatest number of detections (64 out 0f 200; from 0.01 to 20.0 ug/L), Florida, Missouri, and Virginia; wells were sampled without detections in Louisiana (0 out of 3) , Mississippi (0 out of 120) , Oregon (0 out of 44) , and Washington (0 out of 81); dates were not reported. In Florida, bentazon was detected at concentrations of 3.3 to 120 ug/L in 3 of 24 samples collected from four shallow wells located near greens and tees at six golf courses; dates not reported. In the 3700 acre Nomini Creek Watershed, Westmoreland County, VA, bentazon was detected at concentrations of 0.07 to 0.547 ug/L in 5 of 12 wells (4 household wells and 8 monitoring wells). In Missouri, bentazon was detected at concentrations from 0.6 to 1.0 ug/L in 5 out of 266 private rural wells located in three agricultural counties(1).

(1) USEPA/OPP; Reregistration Eligibility Decisions (REDs) Database. Bentazone. EPA 738-R-94-029. Available from, as of Nov 20, 2017: https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1

Hazardous Substances Data Bank (HSDB)

GROUND WATER: Water quality data compiled from the Retrieval (STORET) Data Warehouse and the USGS National Water Information System (NWIS) reports ground water monitoring data. USGS Water Science Center monitoring sites in several states as well as sites such as the Minnesota Department of Agriculture - Pesticide Monitoring report data for bentazon. Select data from the 2010 to 2017 monitoring years follows(1).

Date	No. Detections	Concn (ug/L)
Jan - Dec 2010	42 of 412 samples	0.0008-15.5
Jan - Dec 2011	56 of 536 samples	0.0008-14.1
Jan - Dec 2012	28 of 534 samples	0.00741-12.1

Date	No. Detections	Concn (ug/L)
Jan - Dec 2013	44 of 900 samples	0.36-4.7
Jan - Dec 2014	43 of 810 samples	0.05-6.590
Jan - Dec 2015	36 of 542 samples	0.00504-4.950
Jan - Dec 2016	55 of 740 samples	0.00229-25.900
Jan - Oct 2017	0 of 182 samples	Not detected - MDL 10 ng/L and 0.06 ug/L

*(1) National Water Quality Monitoring Council. Water Quality Data. Characteristics. Bentazon. Available from as of Nov 21, 2017: **https://www.waterqualitydata.us/portal***

Hazardous Substances Data Bank (HSDB)

DRINKING WATER: Bentazon was detected in 4 out of 240 well water samples from rural Illinois, at concentrations ranging from 1.7 to 10 ug/L(1). In the National Survey of Pesticides in Drinking Water Wells, conducted by the U.S. EPA, it was estimated that 7160 rural domestic wells contain bentazon(2). Bentazon was detected in 64 water wells in California between 1975-1991 with a maximum concentration of 20 ug/L(3). Bentazon was detected in well water in rural Missouri at a concentrations of 1 ppb(4). In a U.S. national survey of wells, bentazon was detected in a total of 80 water samples between 1981-1990 with concentrations ranging from 0.1 to 41.89 ug/L(5).

(1) Mehnert E et al; Groundwater Monit Remed 15: 142-9 (1995) (2) Briskin JS; pp. 143-54 in Mech Pestic Mov Groundwater, CRC Press (1994) (3) Lam RHF et al; pp. 15-44 in Water Contamination and Health. Wang RGM, ed., New York, NY: Marcel Dekker, Inc (1994) (4) Sievers DM, Fulhage CD; Ground Water Monit Rev 12: 142-50 (1992) (5) USEPA; Pesticides in Groundwater Database. A Compilation of Monitoring Studies: 1971-1991. National Summary. USEPA Off Pest Programs Prevention Pesticides and Toxic Substances (H7507C) USEPA-734-12-92-001 (1992)

Hazardous Substances Data Bank (HSDB)

For more Environmental Water Concentrations (Complete) data for Bentazon (8 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.2.14 Atmospheric Concentrations

RURAL/REMOTE: Bentazon was not detected in ambient air samples collected weekly over an 8-week period from May to September 2004 at St. Damase located in the mid-watershed of the Yamaska River, Quebec(1).

(1) Aulagnier F et al; Sci Tot Enviro 394: 338-348 (2008)

Hazardous Substances Data Bank (HSDB)

12.2.15 Food Survey Values

Bentazon was not included in the U.S Food and Drug Administration Total Diet Study Market Baskets 2004 through 2005(1).

*(1) US Food and Drug Administration; Office of Analytics and Outreach. Analytical Results. Pesticide Residues and Industrial Chemicals. Available from, as of Nov 21, 2017: **https://www.fda.gov/default.htm***

Hazardous Substances Data Bank (HSDB)

12.2.16 Milk Concentrations

In 2010, bentazone was not detected in bovine raw milk (n=100) from a local farm, and full-fat milk (n=30), half-skimmed milk (n=20), and skimmed milk (n=20) from a local supermarket, near Shenyang Agricultural University, China(1).

(1) Tian H Chemosphere 83: 349-355 (2011)

Hazardous Substances Data Bank (HSDB)

12.2.17 Probable Routes of Human Exposure

Occupational exposure to bentazon may occur through inhalation of dust and dermal contact with this compound at workplaces where bentazon is produced or used. Limited monitoring and use data indicate that the general population may be exposed to bentazon via ingestion of contaminated water. (SRC)

Hazardous Substances Data Bank (HSDB)

13 Associated Disorders and Diseases

- Comparative Toxicogenomics Database (CTD)

Associated Occupational Diseases with Exposure to the Compound

Contact dermatitis, allergic [Category: Skin Disease]

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

14 Literature

14.1 NLM Curated PubMed Citations

PubChem

14.2 Springer Nature References

Springer Nature

14.3 Thieme References

Thieme Chemistry

14.4 Depositor Provided PubMed Citations

PubChem

14.5 Metabolite References

Human Metabolome Database (HMDB)

14.6 Chemical Co-Occurrences in Literature

PubChem

14.7 Chemical-Gene Co-Occurrences in Literature

PubChem

14.8 Chemical-Disease Co-Occurrences in Literature

PubChem

15 Patents

15.1 Depositor-Supplied Patent Identifiers

PubChem

Link to all deposited patent identifiers

PubChem

15.2 WIPO PATENTSCOPE

Patents are available for this chemical structure:

https://patentscope.wipo.int/search/en/result.jsf?inchikey=ZOMSMJKLGFBRBS-UHFFFAOYSA-N

PATENTSCOPE (WIPO)

16 Interactions and Pathways

16.1 Chemical-Target Interactions

- Comparative Toxicogenomics Database (CTD); Toxin and Toxin Target Database (T3DB)

17 Biological Test Results

17.1 BioAssay Results

PubChem

18 Classification

18.1 MeSH Tree

Medical Subject Headings (MeSH)

18.2 ChEBI Ontology

ChEBI

18.3 ChemIDplus

ChemIDplus

18.4 ChEMBL Target Tree

ChEMBL

18.5 UN GHS Classification

UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

18.6 EPA CPDat Classification

- EPA Chemical and Products Database (CPDat)

18.7 NORMAN Suspect List Exchange Classification

- NORMAN Suspect List Exchange

18.8 EPA DSSTox Classification

- EPA DSSTox

18.9 FDA Drug Type and Pharmacologic Classification

National Drug Code (NDC) Directory

18.10 EPA Substance Registry Services Tree

EPA Substance Registry Services

19 Information Sources

FILTER BY SOURCE ALL SOURCES

1. CAS Common Chemistry

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   Bentazon

   https://commonchemistry.cas.org/detail?cas_rn=25057-89-0

2. ChemIDplus

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   Bentazone [BSI:ISO]

   https://pubchem.ncbi.nlm.nih.gov/substance/?source=chemidplus&sourceid=0025057890

   ChemIDplus Chemical Information Classification

   https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

3. EPA Chemicals under the TSCA

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   1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-, 2,2-dioxide

   https://www.epa.gov/chemicals-under-tsca

4. EPA DSSTox

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   https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

   Bentazone

   https://comptox.epa.gov/dashboard/DTXSID0023901

   CompTox Chemicals Dashboard Chemical Lists

   https://comptox.epa.gov/dashboard/chemical-lists/

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   https://echa.europa.eu/substance-information/-/substanceinfo/100.042.335

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   https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/67194

6. FDA Global Substance Registration System (GSRS)

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   https://www.fda.gov/about-fda/about-website/website-policies#linking

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   https://gsrs.ncats.nih.gov/ginas/app/beta/substances/R4S7ZGZ9CT

7. Hazardous Substances Data Bank (HSDB)

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   https://www.nlm.nih.gov/web_policies.html

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   https://pubchem.ncbi.nlm.nih.gov/source/hsdb/3430

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1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-isopropyl-, 2,2-dioxide
https://www.cdc.gov/niosh-rtecs/DK970FE0.html

10. ### ChEBI

Bentazone
http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:3018

ChEBI Ontology
http://www.ebi.ac.uk/chebi/userManualForward.do#ChEBI%20Ontology

11. ### Toxin and Toxin Target Database (T3DB)

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http://www.t3db.ca/toxins/T3D4479

12. ### Comparative Toxicogenomics Database (CTD)

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> http://ctdbase.org/about/legal.jsp

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https://ctdbase.org/detail.go?type=chem&acc=C002003

13. ### Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

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> https://haz-map.com/About

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https://haz-map.com/Agents/3821

14. ### EPA Chemical and Products Database (CPDat)

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> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

Bentazone
https://comptox.epa.gov/dashboard/DTXSID0023901#exposure

EPA CPDat Classification
https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

15. ### EPA Pesticide Ecotoxicity Database

> LICENSE
> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

https://ecotox.ipmcenters.org/

16. ### EU Pesticides Database

Bentazone
https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event=as.details&as_id=451

17. ### NORMAN Suspect List Exchange

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NORMAN Suspect List Exchange Classification
https://www.norman-network.com/nds/SLE/

18. ### EPA Regional Screening Levels for Chemical Contaminants at Superfund Sites

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> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

Bentazon
https://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search

Bentazon
https://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search?tool=rml

19. ### EU REGULATION (EC) No 1272/2008

bentazone (ISO);3-isopropyl-2,1,3-benzothiadiazine-4-one-2,2-dioxide
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1272-20221217

20. ### Hazardous Chemical Information System (HCIS), Safe Work Australia

bentazone (ISO)

http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=355

21. ## Human Metabolome Database (HMDB)

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http://www.hmdb.ca/citing

Bentazone
http://www.hmdb.ca/metabolites/HMDB0248965

HMDB0248965_msms_2226874
https://hmdb.ca/metabolites/HMDB0248965#spectra

22. ## SpectraBase

3-ISOPROPYL-1H-2,1,3-BENZOTHIADIAZIN-4(3H)-ONE, 2,2-DIOXIDE
https://spectrabase.com/spectrum/9DlCHu88Hjk

3-ISOPROPYL-1H-2,1,3-BENZOTHIADIAZIN-(4)-3H-ONE 2,2-DIOXIDE
https://spectrabase.com/spectrum/Gg2opEulxQ3

Bentazone
https://spectrabase.com/spectrum/DSvXVFHY7Cy

Bentazone
https://spectrabase.com/spectrum/1TQZzNtPRlm

BENTAZONE PESTANAL
https://spectrabase.com/spectrum/AZL3OyVudKb

1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-, 2,2-dioxide; 3-Isopropyl-2,1,3-benzothiadiazin-4-one 2,2-dioxide; Bentazon
https://spectrabase.com/spectrum/7BRXeqIzh4e

23. ## Japan Chemical Substance Dictionary (Nikkaji)
http://jglobal.jst.go.jp/en/redirect?Nikkaji_No=J1.875I

24. ## MassBank Europe

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https://github.com/MassBank/MassBank-web/blob/main/MassBank-Project/LICENSE.txt

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https://massbank.eu/MassBank/Result.jsp?inchikey=ZOMSMJKLGFBRBS-UHFFFAOYSA-N

25. ## MassBank of North America (MoNA)

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https://mona.fiehnlab.ucdavis.edu/spectra/browse?query=exists(compound.metaData.name:%27InChIKey%27%20and%20compound.metaData.value:%27ZOMSMJKLGFBRBS-UHFFFAOYSA-N%27)

26. ## NIST Mass Spectrometry Data Center

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https://www.nist.gov/srd/public-law

Bentazone
http://www.nist.gov/srd/nist1a.cfm

27. ## Metabolomics Workbench

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https://www.metabolomicsworkbench.org/data/StructureData.php?RegNo=67425

28. ## NMRShiftDB
https://pubchem.ncbi.nlm.nih.gov/substance/114917522

29. ## Springer Nature
https://pubchem.ncbi.nlm.nih.gov/substance/?source=15745&sourceid=16055031-944177188

30. ## SpringerMaterials

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https://materials.springer.com/substanceprofile/docs/smsid_nbnpurzdaofxohvo

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https://pubchem.ncbi.nlm.nih.gov/substance/?source=22163&sourceid=16055031-944179075

32. ## USDA Pesticide Data Program

Bentazon
https://www.ams.usda.gov/datasets/pdp/pdpdata

33. ## Wikidata

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https://www.wikidata.org/wiki/Q148937

34. **Wikipedia**

Bentazon
https://en.wikipedia.org/wiki/Bentazon

35. **PubChem**
https://pubchem.ncbi.nlm.nih.gov

36. **Medical Subject Headings (MeSH)**

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bentazone
https://www.ncbi.nlm.nih.gov/mesh/67002003

MeSH Tree
http://www.nlm.nih.gov/mesh/meshhome.html

Herbicides
https://www.ncbi.nlm.nih.gov/mesh/68006540

37. **UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)**

GHS Classification Tree
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

38. **ChEMBL**

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http://www.ebi.ac.uk/Information/termsofuse.html

ChEMBL Protein Target Tree
https://www.ebi.ac.uk/chembl/g/#browse/targets

39. **National Drug Code (NDC) Directory**

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FDA Drug Type and Pharmacologic Classification
https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory

40. **EPA Substance Registry Services**

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https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

EPA SRS List Classification
https://sor.epa.gov/sor_internet/registry/substreg/LandingPage.do

41. **PATENTSCOPE (WIPO)**

SID 403405668
https://pubchem.ncbi.nlm.nih.gov/substance/403405668

42. **NCBI**
https://www.ncbi.nlm.nih.gov/projects/linkout

Attachment B

IRIS File

Bentazon (Basagran); CASRN 25057-89-0

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Bentazon (Basagran)

File First On-Line 03/03/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/02/1998
Inhalation RfC (I.B.)	message	03/02/1998
Carcinogenicity Assessment (II.)	yes	03/02/1998

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is

essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
	NOAEL: 3.2 mg/kg bwt/day	100	1	3.0 E-2 mg/kg/day
Confidence -- Medium **Note: 0.032 is rounded down to 0.03 mg/kg bwt/day**				
(1) Blood loss into the gastrointestinal tract	NOAEL Reported - 3.2 mg/kg bwt/day Adjusted - 3.2 mg/kg bwt/day			
(2) Coagulation defect in male and female dogs.	LOAEL Reported - 13.1 mg/kg bwt/day Adjusted - 13.1 mg/kg bwt/day			
Study Type - 1 year dog feeling study - reference -- Allen et al., 1989				
Dose-related increase in red areas (presumed blood) in feces, coagulation defect	Defined Dose Levels: NOAEL --- 100 ppm NOAEL --- (ADJ) -- 3.2 mg/kg bwt/day LOAEL --- 400 ppm LOAEL --- (ADJ) -- 13.1 mg/kg bwt/day			

*Conversion Factors: none

I.A.2. Principal and Supporting Studies (Oral RfD)

Allen et al., 1989. 52-week oral toxicity (feeding) study with bentazon technical (ZST No. 86/48) in the dog. Amendment (MRID No. 410549-01, 41123001, HED Doc. No. 008079). Unpublished study prepared by RCC Research and Consulting Co. AG. Available from US EPA. Write to Freedom of Information Office , US Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460.

Groups of beagle dogs (6/sex/dose) were fed diets containing 0, 100, 400, or 1,600 ppm (average intake of test material: 0, 3.2, 13.1, and 52.3 mg/kg bwt/day) bentazon technical for 1 year. Animals received 300 g of repelleted standard Kliba No. 335 dog maintenance feed for 3 h daily and water was provided ad libitum.

Body weight gains for the test animals were compared by means of t-tests for various periods of dosing. The mean percent body weight gains were slightly decreased at 400 ppm compared to controls, but no statistically significant differences in percent body weight gain were found (i.e., $p < 0.05$) for any period of dosing at 400 ppm.

Clinical signs were mostly limited to the high-dose group (1,600 ppm); there was a suggestive dose-related increase in the incidence of males with feces containing red areas (none at 0 and 100 ppm, 1/6 at 400 ppm, and 2/6 at 1,600 ppm); however, the frequency of the occurrences was not provided. Although the animal incidences of 1/6 (16.6%) at the mid-dose level and 2/6 (33.3%) at the high-dose level versus 0% in the controls lack statistical significance (owing to the small number of animals), this dose-related effect is considered of biological significance when considered with the toxic effects of bentazon on blood coagulation in mice, rats, and another study in dogs (BASF AG, 1970). In male beagles, the partial thromboplastin time (PTT) was elevated ($p < 0.05$) at 1,600 ppm (49.7 mg/kg bwt/day). Therefore, in view of the dose-dependent presence of feces with red areas (though not chemically confirmed to be blood) in dogs fed bentazon at 400 ppm (13.3 mg/kg bwt/day) and 1,600 ppm (49.7 mg/kg bwt/day), and the absence of red areas in feces of animals at 0 and 100 ppm (3.2 mg/kg bwt/day), it is difficult to discount the presence of feces with red areas in mid-dose male dogs as not being treatment related. Therefore, the LOAEL of bentazon in beagle dogs should be established at 400 ppm (13.1 mg/kg bwt/day), based on possible adverse effects on blood coagulation or blood loss in the intestinal tract in male beagles. The NOAEL appears to be 100 ppm (3.2 mg/kg bwt/day).

From the studies provided, one can determine that the longer studies with lower dosages provide appropriate data with which to establish a dose-response relationship. The effect considered most critical in the studies provided was that of the derangement of the hemostasis mechanism because exposure resulted in a significant 40% reduction in hemoglobin, 30%

reduction in red blood cell counts, and 33% reduction in hematocrits compared to control group values in the shorter 13- week study at 75 mg/kg bwt/day. Several other effects were also considered in establishing the appropriate endpoint for an RfD and included the loss in body weight, the effects on the liver, and even the prostatitis noted in one of the earlier studies. Prostatitis in the subchronic, 90-day dog study occurred at 7.5 mg/kg bwt/day with an NOAEL of 2.5 mg/kg bwt/day, but is not considered to be a significant effect because the same effect was not found in a larger (6/sex/dose) and longer 1-year study that did not negate the LOAEL of 7.5 mg/kg bwt/day but raised the NOAEL with some degree of certainty because of the lack of effect seen at a slightly higher dosage (3.2 mg/kg bwt/day). However, the dose level associated with the clotting times and intestinal blood loss problems in the male dog was considered to be the most critical and provided the lowest and most supportable NOAEL in the data set.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 100.

The uncertainty factor of 100 reflects a default factor of 10 for interspecies extrapolation and a similar default factor of 10 for intraspecies variability (Lehman and Fitzhugh, 1954).

MF = 1

Essentially a full database and adequately conducted studies were present and no additional modifying factors were added.

The further addition of modifying factors to provide added protection to the newborn or young who might be exposed to bentazon was not needed. This lack of need was due to several factors: the data on the newborn and young did not indicate that they were significantly more sensitive than the adults in the same study, toxicity to the development of the fetus and young was of a general growth toxicity, the NOAELs for the studies with data on the young were so much higher than the NOAEL in the chronic dog study, and the fact that dogs appeared to be somewhat more sensitive to the effects of bentazon than were rodents.

I.A.4. Additional Studies/Comments (Oral RfD)

(1) 1-Year feeding -- dog. Principal study -- see previous description (Allen et al., 1989) (submitted to support registration).

(2) 2-Year feeding/carcinogenicity -- rat (Takehara and Tajima, 1984) (submitted to support registration).

Groups of Fischer 344/Du rats (70/sex/dose with a 6- and 12-month interim sacrifice of 10/sex/dose) were fed bentazon in the diet for 2 years at dose levels of 0, 200, 800, and 4,000 ppm (male: 0, 9, 35, and 180 mg/kg bwt/day; female: 0, 11, 45, and 244 mg/kg bwt/day). Dose selection was based on 1-month study in which rats were administered bentazon at dose levels of 5,000 and 10,000 ppm. Some of the rats receiving 10,000 ppm died showing hemorrhagic lesions. Animals fed 5,000 ppm developed hemorrhagic lesions in the urogenital organs.

Mean body weights of both high-dose males and females were significantly ($p < 0.05$) lower than controls, in general, from week 5 onward. In males receiving 800 ppm, body weights were significantly ($p < 0.05$) lower than controls for most weeks between weeks 19-36. In females receiving 800 ppm, mean body weights were significantly lower than control only on weeks 60 and 65. Compound-related reductions in food consumption were observed in mid- and high-dose males. No compound-related changes in food consumption were observed for female rats at any dose levels. Weekly mean water consumption was significantly ($p < 0.05$) increased in high-dose male and female rats throughout most the study. For mid-dose animals, mean water intake was sporadically increased in males and females.

For animals sacrificed at 24 mo, urinary specific gravity was lower in high-dose animals as compared to controls, but urine volume was either similar to or significantly ($p < 0.001$) less (in females) than controls.

Absolute and relative mean thyroid weights were significantly ($p < 0.05$) decreased at 6 and 12 mo in mid- and high-dose males. A dose-dependent decrease in absolute and relative mean thyroid weights was suggested by the data in females at 12 mo. However, only the absolute thyroid weight in the high-dose group was significantly ($p < 0.05$) reduced when compared to controls. No significant differences in thyroid weights were observed at 24 mo. Absolute liver and spleen weights were significantly ($p < 0.05$) decreased in high-dose males at 6, 12, and 24 mo. Relative weights were significantly decreased at 6 and 24 mo.

Mean platelet counts were significantly ($p < 0.01$) decreased in mid- and high-dose males and high-dose females at 6 mo. Prothrombin times (PT) and partial thromboplastin times (PTT) were significantly ($p < 0.01$) longer than control values in high-dose (4,000 ppm) males at 6, 12, and 24 mo. Prolonged PTTs were also observed at 12 mo in mid-dose males and females and high-dose females. These alterations in coagulation were considered to be compound related.

Based on the effects observed at the mid-dose, the NOAEL and LOAEL values for systemic toxicity appear to be 200 ppm (male: 9 mg/kg bwt/day; female: 11 mg/kg bwt/day) and 800 ppm (male: 35 mg/kg bwt/day; female: 45 mg/kg bwt/day), respectively.

(3) 2-Generation reproduction -- rat (Suter et al., 1989) (submitted in support of registration).

In a two-generation reproduction study, groups of Wistar/Han rats (25/sex/dose) were fed diets containing bentazon technical at dosage levels of 0, 200, 800, and 3,200 ppm (approximately 0, 15, 62, and 249 mg/kg bwt/day). Mean test material intake ranged from 15 to 238 and from 17 to 269 mg/kg bwt/day for F0 males and females, respectively, and from 14 to 227 and from 16 to 262 mg/kg bwt/day for F1 males and females, respectively, during the premating periods.

Weight losses in dams during the lactation periods of both generations show trends toward significant reductions at the highest dose level, though the weight loss was less than 10% of the control group values. Significantly decreased food consumption was observed in the F1 generation among high-dose females during the premating period and the beginning of the gestation period. A significant trend toward reduced food consumption was observed in the F1 generation during study days 1-8 and 22-29 and on gestation day 0-7.

In the F0 generation, increased incidences were seen in kidney mineralization (1/25 and 3/25 for control and high-dose males, respectively) and liver microgranuloma (7/25 and 16/25 for control and high-dose males, respectively). Also in the F1 generation high-dose males, increased incidences were seen in mineralization of the kidneys (1/25 and 6/25 for control and high-dose males, respectively). Because no historical control data were submitted, the relevance of these data cannot be determined.

No compound-related adverse effects were observed on fertility, implantation sites, postimplantation loss, and offspring survival. Statistically significant and probably biological significant reductions in pup weights and pup weight gains were observed at the high dose levels. Although primarily observed in the P generation at days 4 and 7 (10%-20%), pup weight gains were reduced throughout lactation (10%-19%) in the 3,200 ppm dose group of the F1 generation.

Based on reduced food consumption and histopathological findings among high-dose animals, the LOAEL for parental toxicity is 3,200 ppm (249 mg/kg bwt/day). The NOAEL for parental toxicity is 800 ppm (62 mg/kg bwt/day).

Based on reduced pup weights and pup weight gains, the LOAEL for reproductive toxicity is 800 ppm (62 mg/kg bwt/day). The NOAEL for reproductive toxicity appears to be 200 ppm (15 mg/kg bwt/day).

(4) Developmental toxicity -- rat (Becker et al., 1986a) (submitted in support of registration).

In a dose-ranging study, oral administration of technical bentazon (0, 100, 200, and 300 mg/kg bwt/day) to rats during days 6-15 of pregnancy did not result in any increase in mortality, observable clinical changes, or gross pathology among the treated groups as compared to controls. There was no consistent, compound-related effect on maternal body weight or food consumption. At the highest dose tested there was an increase in percent of embryonic and fetal absorption over control values (primarily fetal in nature), with surviving fetal body weights generally lower than body weights of controls. Based on the findings in this study, dose levels were established in the full developmental toxicity study.

In the main developmental toxicity study, oral administration of technical bentazon at dosage levels of 0, 40, 100, and 250 mg/kg bwt/day to pregnant Wistar rats during days 6-15 of gestation did not produce any consistent signs of systemic maternal toxicity such as clinical signs or symptoms, mortality, changes in mean body weight, or decreases in food consumption. Based on these findings, the NOAEL for maternal toxicity is greater than or equal to 250 mg/kg bwt/day.

At the highest dose tested, bentazon produced an increase in postimplantation loss (fetal resorptions, but no increase in embryonic resorptions). This was accompanied by a depression in the body weights of those fetuses surviving until day 21 sacrifice. It also produced an effect on the rate of growth, as evidenced by a decrease in the rate of ossification in the phalangeal nuclei of fore and hind limb digits, the 5th sternebra, and cervical vertebra. A decrease in body weight in conjunction with delays in tissue maturation suggests that bentazon is a general fetal systemic toxicant. Based the above effects, the LOAEL for developmental toxicity is 250 mg/kg bwt/day. The NOAEL for developmental toxicity appears to be 100 mg/kg bwt/day.

(5) Developmental toxicity -- rabbit (Becker et al., 1986b) (submitted in support of registration).

In a dose-ranging study, Chinchilla rabbits (3/dose group) were administered technical bentazon by gavage daily at dose levels of 0, 150, 300, and 450 mg/kg bwt/day) from day 6-18 of post coitus.

Two of three does were pregnant in all dose groups. The high-dose group had one doe in which no live fetuses were observed, only embryonic resorptions. The mean body weights of pregnant does in the 300 mg/kg bwt/day dose group were initially lower (because of one low-weight rabbit) than other dose groups and remained depressed during the study. Based on differences in mean body weight gains (%), there does not appear to be any compound-related effect on weight gain. However, the lack of an adequate number of pregnant does makes these comments quite tentative in nature. Food consumption data have the same limitations as for body weight gain, with the additional factor that one of the control rabbits had spillage of food

during day periods of 15-19, 19-24, and 24-28.

Preimplantation losses (%) were higher in the high-dose group as compared to the controls (20% vs. 0%). The mean number of fetuses/litter decreased in the high-dose group as compared to the control or other treatment groups (7.5, 8.5, 8.0, and 2.0 for the control, low-, mid-, and high-dose groups, respectively).

Mean fetal weights (g) appeared to be lower in all treated groups as compared to the controls (40.3, 31.5, 34.2, and 32.3 for the control, low-, mid-, and high-dose groups, respectively). The study authors noted that this difference is an artifact of the high mean body weight of the control fetuses because historical control weights (34.6 g/vehicle control animals, 33.4 g/untreated control animals) were similar to the treated groups.

It is concluded that bentazon produced a significant increase in embryonic resorptions at the highest dose tested (450 mg/kg bwt/day) as compared to the control group. Mean body weight and food consumption data were inadequate to permit a dose-related systemic toxicity response to be determined.

In the main developmental toxicity study, oral administration of technical bentazon at dosages of 0, 75, 150, and 375 mg/kg bwt/day to female Chinchilla rabbits during the period of major organogenesis (days 6-18) did not produce any appreciable evidence of compound-related maternal toxicity as measured by changes in mean body weight, mean body weight gains, corrected body weight gain, food consumption, or overt clinical signs except for the observation of one doe with a partial abortion, embryonic resorptions, and no living fetuses. This observation is probably compound related because 2/3 does treated with bentazon during the dose-ranging study at a higher dose (450 mg/kg/day) produced almost complete resorption of the observed embryos. Therefore, the LOAEL for maternal toxicity was set at 375 mg/kg bwt/day. The NOAEL for maternal toxicity appears to be 150 mg/kg bwt/day.

There were no significant effects of bentazon administration on mean resorptions/doe, mean numbers of liver fetuses/doe, mean fetal weights, or mean sex ratios in those animals fully evaluated at day 29 of sacrifice. No abnormal developmental toxicity was observed at any dose level for gross, visceral, or skeletal findings. The developmental NOAEL appears to be 375 mg/kg bwt/day.

Other Data Reviewed:

(6) 13-week feeding -- dog (BASF AG, 1970) (submitted in support of registration).

Groups of beagle dogs (3/sex/dose) were administered bentazon orally for 13 weeks at dose

levels of 0, 100, 300, 1,000, and 3,000 ppm (0, 2.5, 7.5, 25, and 75 mg/kg bwt/day).

Dogs receiving 3,000 ppm produced a variety of symptoms, and 1 of 3 males and 2 of 3 females at that dose died during the 13 weeks of the study. Dogs tended to be sedated, eventually lost weight, became cachectic, developed diarrhea, frequently vomited, had skin lesions, stomatitis, conjunctivitis, and the general appearance of severely compromised health. The 3 males at 3,000 ppm exhibited fresh blood in their stools by the end of the study. Several urinalysis, hematological, and blood chemistry tests confirmed the picture of general ill health. In particular, the blood chemistry tests suggested pathology of the liver, and this effect was borne out by daily observations, gross pathology (e.g., weight loss, cachexia, stomatitis, and other areas of inflammation and sores on skin and surface membranes), and microscopic inspection (e.g., fatty infiltration of heart and liver, necrotic congestion of the liver, albuminous swelling of the kidneys, etc.). Prostatitis was observed in all three 3,000 ppm males, in 1 of 3 males in the 1,000 ppm group, and one 300 ppm male. One of the three 3,000 ppm males and one 1,000 ppm male had empty epididymal ducts. Only the latter animal had positive signs of epididymal maturation deficiency. On the basis of observed prostatitis, a provisional LOAEL of 300 ppm (7.5 mg/kg bwt/day) can be established, with the associated NOAEL appearing to be 100 ppm (2.5 mg/kg bwt/day).

(7) 13-week feeding -- rat (Tennekes et al., 1987) (submitted in support of registration).

Groups of Wistar rats (10/sex/dose) were administered bentazon in diet for 13 weeks at dose levels of 0, 400, 1,200, and 3,600 ppm (male: 0, 25.3, 77.8, and 243.3 mg/kg bwt/day; female: 0, 28.9, 86.1, and 258.3 mg/kg bwt/day). An additional 10 animals/sex were placed in the control and high-dose groups and used for a 28-day recovery group.

Three deaths (1 male and 2 females) occurred in the high-dose group during the course of the study. Female but not male body weights were significantly depressed as compared to controls in the high-dose group, with the mean weights remaining somewhat lower in the recovery period. Males had a minimal but consistent increase in food consumption. Bentazon appears to produce an inconsistent effect (between sexes) upon thromboplastin time (PT) and prothrombin time (PTT) in the high-dose groups as compared to controls, with males having a statistically significant increase in these parameters and females having a significant depression (PT only). These values returned to control levels in the recovery period. Reversible changes in clinical chemistries were observed in male and female rats during compound administration and recovery. No statistically significant increases in histopathological changes were observed. However, in the females there is a suggestion of an increase in lung thrombi and dilation of the uterine horns in the high-dose group as compared to controls.

Based on the effects observed at the highest dose tested, the LOAEL for systemic toxicity is 3,600 ppm (male: 243.3 mg/kg bwt/day; female: 258.3 mg/kg bwt/day). The NOAEL for systemic toxicity appears to be 1,200 ppm (male: 77.8 mg/kg bwt/day; female: 86.1 mg/kg bwt/day).

Data Gaps: None

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The study design of the principal study was adequate and complete. However, data on test material stability analysis could not be verified, there was a possibility that unthrifty animals were used, and the presence of blood in the feces was not chemically proven. Therefore, the principal study is given a medium confidence rating. The database is given a high confidence rating because there are no data gaps and additional studies support the principal study. The use of a medium confidence in the principal study and a high confidence in the database supports a medium-to-high confidence in the RfD.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is presented in the Toxicological Review of Bentazon (CAS No. 25057-89-0). (EPA, 1998)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to US EPA, 1998, Toxicological Review of Bentazon. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — None

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Bentazon (Basagran) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

I.B.6. EPA Documentation and Review of the Inhalation RfC

No data available with which to establish an RfC value for bentazon.

Other EPA Documentation — None

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Bentazon (Basagran) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

N.A.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimated in terms of either risk per µg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under EPA's 1986 Guidelines for Carcinogen Risk Assessment, Bentazon would be classified as *evidence of non-carcinogenicity for humans*, or a Group E chemical. Under EPA's proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996), Bentazon would be characterized as *not likely to be carcinogenic to humans by any route of exposure.* Additionally, the Health Effects Division, Office of Pesticide Programs cancer peer review committee has concluded after evaluating the known and submitted studies that the animal bioassays were essentially negative for a carcinogenic effect from chronic feeding, and under the older classification system the chemical was classed as an E for carcinogenic potential (U.S. EPA, 1992).

The metabolic pathways of bentazon and the handling of it by the mammalian system are well understood and do not produce any significant suspect reactive species. The mutagenicity studies do not indicate a mutagenicity hazard from the chemical and structure-activity comparisons to similar chemical structures are negative for significant effects regarding carcinogenic potential.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

The Agency is unaware of any data available for review.

II.A.3. Animal Carcinogenicity Data

Studies were considered adequate for evaluation of the carcinogenic potential in animals. The results were considered to not be indicative of a hazard to test animals.

1. Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon in rats. Core grade: guideline, (Takehara, et al. ,1984) (data submitted to support registration).

Groups of Fischer 344/Du rats (50/sex/dose with a 6 and 12 month interim sacrifice each containing an additional 10/sex/dose) were fed bentazon in the diet for 2 years at dose levels of 0, 200, 800, and 4000 ppm (Male: 0, 9, 35, and 180 mg/kg/day; Female: 0, 11, 45, and 244 mg/kg-day). Dose selection was based on a supplementary 1-month study in which rats were administered bentazon at dose levels of 5000 and 10,000 ppm. Some of the rats receiving 10,000 ppm died showing hemorrhagic lesions. Animals fed 5000 ppm developed hemorrhagic lesions in the urogenital organs.

Mean body weights of both (4000 ppm) high-dose males and females were significantly ($p < 0.05$) lower than controls, in general, commencing at week 5. In males receiving 800 ppm, body weights were significantly ($p < 0.05$) lower than controls for most weeks between weeks 19-36. Compound-related reductions in food consumption were also observed in mid- and high-dose males. No compound-related changes in food consumption were observed for female rats at any dose levels.

Absolute and relative mean thyroid weights were significantly ($p < 0.05$) decreased at 6 and 12 months in mid- and high-dose males. A dose-dependent decrease in absolute and relative mean thyroid weights was suggested by the data from females at 12 months. However, only the absolute thyroid weight in the high-dose group was significantly ($p < 0.05$) different from control. No significant differences in thyroid weights in the females were observed at 24 months. Absolute liver and spleen weights were significantly ($p < 0.05$) decreased in high-dose males at 6, 12 and 24 months and relative weights were significantly decreased at 6 and

24 months. There was little difference in longevity of the treated animals compared to controls.

Neoplastic findings in the animals which either died or were sacrificed *in extremis* and those that were sacrificed at termination of the study indicate that pheochromocytomas were significantly increased in females fed 4000 ppm of bentazon in the diet. There was an apparent dose-response with this finding. Further information on the historical incidence of this tumor in the testing laboratory indicated that the apparent increase was well within the 13% control values reported by the testing laboratory. Females in the 800 and 4000 ppm dosage groups exhibited a slight increase in endometrial polyps with 36% and 24% respectively when compared to a 20% incidence in controls. These incidence rates were not statistically significantly increased. Chromophobe adenomas were statistically significantly increased in the females only in the 200 ppm dosed group 18/29 (62%) when compared to 11/31 (35%) in controls. These incidences are not considered to be biologically significant due to the lack of a dose response at higher doses. This study has been judged to be negative for a carcinogenic response to the exposure in the diet of male and female rats.

Based on the effects observed at the mid-dose, the NOAEL and LOAEL for systemic toxicity are 200 ppm (Male: 9 mg/kg-day; Female: 11 mg/kg-day) and 800 ppm (Male: 35 mg/kg-day; Female: 45 mg/kg-day), respectively.

2. Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon, reg. No. 51 929 (ZNT No. 91/273), in mice. Core grade: Guideline. (Tajima, et al., 1984). (submitted in support of registration).

Bentazon was fed to male and female B6C3F1 mice at levels of 0, 100, 400, or 2000 ppm in the diets for 2 years. There were increased prothrombin times in males that received 400 or 2000 ppm. The increased clotting times were accompanied by an increase in hemorrhage in the liver and heart of the high dose males which died during the study. There was an increase in calcification of the tunica albuginea of the testes and an increase in islet cell hyperplasia of the pancreas in males receiving 400 or 2000 ppm of bentazon. There was a transient, slight decrease in mean body weights in males at intervals between weeks 7 and 23 and increases in organ weights of kidneys, thyroids and pituitaries in mid and high-dosed males. There were no effects on body weights from exposure to the chemical in dosed females. Increased liver weight and relative kidney weights were noted in mid-dose females.

Reports of three pathologists reading the histopathological slides of livers were evaluated as well as the historical control data for the liver tumors in the B6C3F1 mice. It was concluded that there was no real increase in the incidence of hepatocellular carcinomas and the chemical should be classified as a Group E (evidence of non-carcinogenicity for humans), based upon a

lack of evidence of carcinogenicity in two adequate animal species studied (U.S. EPA. 1992). It should be emphasized, however that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

II.A.4. Supporting Data for Carcinogenicity

Mutagenicity:

Overall, the weight of the evidence does not suggest a significant mutagenicity concern for bentazon. Acceptable tests have been conducted in three categories: gene mutations, structural chromosome aberrations, and other genotoxic effects (DNA damage and repair) (U.S. EPA, 1991).

1. Bentazon was negative in reverse mutation assays with Salmonella strains (+S9) at doses of 20-5,000 ug/plate and in E. coli WP2 uvrA (+S9) at levels of 10-1,000 ug/plate (Engelhardt, 1985 a).

2. Bentazon was negative in the CHO/HGPRT forward mutation assays with and without rat liver S9 mix at concentrations of 100-5,000 ug/mL (DenBoer, 1985; Mullerschon, 1991).

3. In the mouse micronucleus test, bentazon did not cause a significant increase in micronuclei in NMRI mice of either sex at dosages between 200 and 800 mg/kg (Engelhardt, 1985 b).

4. Bentazon was negative for unscheduled DNA synthesis in an acceptable UDS/primary mouse hepatocyte assay at doses of 2.5 and 502 ug/mL (Cifone, 1985).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

No data available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

No data available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. Environmental Protection Agency. (1998) Toxicological Review of Bentazon (CAS No. 25057-89-0).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to US EPA 1998, Toxicological Review of Bentazon. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Bentazon (Basagran) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0

VI.A. Oral RfD References

Allen, TR; Frei, TH; et al. (1989) 52-week oral toxicity (feeding) study with bentazon technical (ZST No. 86/48) in the dog. Amendment (MRID No. 410549-01, HED Doc. No. 008079). Unpublished study prepared by RCC Research and Consulting Co. AG.

BASF AG. (1970) Authors Zeller and Kirsch; 13-week toxicity of 3-isopropyl 2,1,3-benzothiadiaxinone-(4)-2,2-dioxide to beagles when administered with the food. MRID No. 00091058, HED Doc. No. 000394, 0003912. Unpublished study prepared by BASF AG.

Becker, HD; Frei, D; Vogel, W; et al. (1986a) Embryotoxicity (including teratogenicity) study with bentazon technical in the rat. Unpublished study (No. 87/5004) prepared by RCC Research and Consulting Co. AG.

Becker, H; Mueller, E; Vogel, W; et al. (1986b) Embryotoxicity (including teratogenicity) study with bentazon technical in the rabbit. (MRID No. 40114202, HED Doc. No. 006231). Unpublished study (No.87/5003) prepared by RCC Research and Consulting Co. AG.

Lehman, AJ; Fitzhugh, OG. (1954) 100-fold margin of safety. Assoc Food Drug Off US Q Bull 18:33-35.

Suter, P; et al. (1989) Report on the two-generation reproduction study with bentazon technical (ZST No. 86/48) in the rat. MRID No. 4100549-02, HED Doc. No. 008079.

Takehara, K; Tajima, M. (1984) Studies on the 24-month chronic toxicity of bentazon in rats. MRID No. 00142831, 00142833, 40871701, 40871702, HED Doc. No. 006459, 007247. Unpublished translation prepared by Nippon Institute for Biological Sciences.

Tennekes, H; Horst, K; Leutkemeier, H; et al. (1987) Report on the 13-week oral toxicity (feeding) study with bentazon technical in the rat. MRID No. 40222201, HED Doc. No. 006421. Unpublished study prepared by RCC Research and Consulting Co. AG.

U.S. Environmental Protection Agency (1998) Toxicological Review of Bentazon (CAS No. 25057-89-0) in Support of Summary Information on Integrated Risk Information System (IRIS). Available online at http://www.epa.gov/iris.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Cifone, M. (1985) Evaluation of bentazon in the in vitro mouse primary hepatocyte unscheduled DNA synthesis assay. Unpublished report prepared by Litton Bionetics.

DenBoer, W. (1985) Mutagenicity evaluation of bentazon technical (84-140) in the CHO/HGPRT forward mutation assay. Unpublished study prepared by Litton Bionetics, Inc.

Engelhardt, G. (1985 a) Report on the study of bentazon in the Ames Salmonella/microsome plate assay and reverse mutation assay - E. coli WP2 uvrA. Unpublished study prepared by BASF AG.

Engelhardt, G. (1985b) Cytogenetic investigations in NMRI mice after a single oral administration of bentazon: Micronucleus test. Unpublished study prepared by BASFAG.

Mullerschon, H. (1991) Gene mutation assay in Chinese Hamster Ovary Cells in vitro with bentazon. Unpublished study prepared by Cytotest Cell Research.

Tajima, M., K. Takehara, M. Itabashi, et al. (1984) Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon, reg. No. 51 929 (ZNT No. 91/273), in mice.

Takehara, K. and M. Tajima. (1984). Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon in rats.

U.S. Environmental Protection Agency. (1992) First and Second Peer Review of Bentazon. Memorandum from James Rowe, Alberto Protzel and George Ghali to Joanne Miller dated January 14, 1992.

U.S. Environmental Protection Agency (1996). Proposed Guidelines for Carcinogen Risk Assessment. Federal Register 61(79):17960-18011.

U.S. Environmental Protection Agency (1998) Toxicological Review of Bentazon in Support of Summary Information on Integrated Risk Information System (IRIS). Available online at http://www.epa.gov/iris.

VII. Revision History

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

Date	Section	Description
03/02/1998	I.A.,II.,VI.	New RfD, Cancer Assessment, RfC message
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

- 25057-89-0
- BAS 351-H
- BASAGRAN
- BENDIOXIDE
- Bentazon
- BENTAZONE

- 1 H-2,1,3-BENZOTHIADIAZIN-4 (3H)-ONE-2,2-DIOXIDE, 3-ISOPROPYL-
- 3-ISOPROPYL-2,1,3-BENZOTHIADIAZINON-(4)-2,2-DIOXID
- 3-ISOPROPYL-1 H-2, 1-3-BENZOTHIADIAZIN-4(3H)-ONE-2,2-DIOXIDE
- 3-(1-METHYLETHYL)-1H-2,1,3-BENZOTHIAZAIN-4(3H)-ONE,2,2-DIOXIDE

Derivation of Proposed Groundwater

Interim Maximum Allowable Concentration (IMAC)

Boscalid

1. Introduction

North Carolina regulations [15A NCAC 02L.0202 (c)] allow a party to petition for the establishment of an Interim Maximum Allowable Concentration (IMAC) for a substance lacking a groundwater standard. In the absence of a groundwater standard for boscalid, an IMAC is proposed in this document. The IMAC was developed in accordance with the North Carolina Department of Environmental Quality (NCDEQ) Division of Water Resources Standard Operating Procedure for Establishing IMACs (NCDEQ, 2022).

Per the regulations [15A NCAC 02L.0202 (c)], the groundwater quality standard (GWQS) is the lowest of the following:

1. Systemic threshold concentration;
2. Concentration corresponding to an incremental lifetime cancer risk of 10^{-6};
3. Taste threshold limit value;
4. Odor threshold limit value;
5. Maximum contaminant level (MCL);
6. National secondary drinking water standard.

The regulations [15A NCAC 02L.0202 (c)] state that the following sources, in order of preference, be used in establishing the above levels:

1. The United States Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS).
2. Health Advisories (USEPA Office of Drinking Water).
3. Other health risk assessment data published by USEPA.
4. Other relevant, published health risk assessment data, and scientifically valid peer-reviewed published toxicological data.

Section 2 provides an overview of boscalid and a summary of available data. Risk-based GWQS are calculated in Section 3, and the proposed IMAC is presented in Section 4. References are provided in Section 5.

2. Boscalid Data

According to a USEPA Fact Sheet (USEPA, 2003), boscalid (CAS No. 188425-85-6) is a registered fungicide for use on food crops. It is a white crystalline powder with a faint smoky odor (USEPA, 2003). The Fact Sheet, provided in **Attachment A**, indicates that boscalid has low toxicity for oral, dermal, inhalation, primary eye irritation and primary skin irritation. In animal studies, effects associated with boscalid exposure included body weight changes, liver effects, and thyroid effects. However, USEPA's exposure and risk assessments found no unacceptable risks. The Fact Sheet provides a summary of test

results and a summary of chemical and physical properties. The chemical structure and chemical properties are provided in **Attachment B** (PubChem, 2023).

An oral reference dose (RfD) of 0.22 milligrams per kilogram body weight per day (mg/kg-day) is available for boscalid from the USEPA Office of Chemical Safety and Pollution Prevention, documented in a 2019 memorandum (USEPA, 2019, provided in **Attachment C**). The RfD is based on chronic and sub-chronic rat studies. A lowest observed adverse effect level (LOAEL) of 110 mg/kg-day was identified for thyroid lesions. A no observed adverse effect level (NOAEL) of 22 mg/kg-day was established based on the study. USEPA applied uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies extrapolation to derive the RfD based on the NOAEL (22 mg/kg-day ÷ 100). Boscalid was classified with "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" (USEPA, 2019). Therefore, a cancer slope factor was not derived.

USEPA has not established an MCL or a secondary drinking water standard (USEPA, 2023), or a health advisory level (HAL; USEPA 2018) for boscalid. A drinking water "human health benchmark for pesticides" (HHBP) of 1.3 milligrams per Liter (mg/L) is available from the USEPA (2021a). The HHBP is based on the RfD of 0.22 mg/kg-day established by USEPA and assumes daily exposure to boscalid in drinking water for a lifetime. USEPA calculated the HHBP using a body weight normalized drinking water intake rate of 0.0338 L/kg-day (USEPA, 2021b). No odor or taste thresholds have been established.

3. Derivation of Risk-Based GWQS

A systemic threshold concentration for boscalid was derived in accordance with 15A NCAC 02L.0202(c)(1) as follows:

Derivation of Noncancer Systemic Threshold Concentration for Boscalid			
Parameter	**Value**	**Units**	**Notes/Source**
Oral Reference Dose (RfD)	0.22	mg/kg-day	USEPA, 2021a
Body Weight (WT)	70	kg	NCAC 02L.0202 (c)(1)
Relative Source Contribution (RSC)	0.2	unitless	NCAC 02L.0202 (c)(1). Value for organics
Water Ingestion Rate (WI)	2	L/day	NCAC 02L.0202 (c)(1)
Conversion Factor (CF)	1000	µg/mg	NCAC 02L.0202 (c)(1)
Noncancer Systemic Threshold Concentration	1.54	mg/L	[(RfD x WT x RSC)/WI] x CF

As boscalid is not classified as carcinogenic, there is no cancer slope factor and a GWQS for the cancer endpoint is not calculated.

4. Recommended IMAC

The table below summarizes the available thresholds for boscalid.

Selection of Proposed IMAC for Boscalid			
Parameter	**Value**	**Units**	**Notes/Source**
Noncancer Systemic Threshold Concentration	1.54	mg/L	Calculated above
Concentration corresponding to Cancer Risk 10^{-6}	--	--	Not carcinogenic
Taste Threshold Value	--	--	No threshold identified
Odor Threshold Value	--	--	No threshold identified
Maximum Contaminant Level (MCL)	--	--	USEPA (2023)
National Secondary Drinking Water Standard	--	--	USEPA (2023)
Lifetime Health Advisory Level (HAL)	--	--	USEPA (2018)
Human Health Benchmark for Pesticides (HHBP)	1.3	mg/L	USEPA (2021a)
Proposed Interim Maximum Allowable Concentration (IMAC)	1.3	mg/L	Lowest value selected; USEPA HHBP

Based on the review and calculations provided here, an IMAC of 1.3 mg/L is proposed for boscalid, based on USEPA's HHPB.

5. References

NCDEQ. 2022. Division of Water Resources Standard Operating Procedure for Establishing Interim Maximum Allowable Concentrations (IMACs) per 15A NCAC 02L .0202 (c). Revised April.

PubChem. 2023. Boscalid C18H12Cl2N2O. Compound Summary. https://pubchem.ncbi.nlm.nih.gov/compound/213013. Accessed 5/9/23.

USEPA. 2018. 2018 Edition of the Drinking water Standards and Health Advisories Tables. EPA 822-F-18-001. Office of Water. USEPA. March.

USEPA. 2019. Boscalid. Human Health Risk Assessment for Registration Review. Office of Chemical Safety and Pollution Prevention. September 25.

USEPA. 2021a. 2021 Human Health Benchmarks for Pesticides. https://www.epa.gov/sdwa/2021-human-health-benchmarks-pesticides. Accessed June 2023.

USEPA. 2021b. Updated Human Health Benchmarks for Pesticides: Updated 2021 Technical Document.

USEPA. 2023. National Primary Drinking Water Regulations and Secondary Drinking Water Regulations. https://www.epa.gov/sdwa. Accessed June 2023.

Attachment A

USEPA Pesticide Boscalid Fact Sheet

United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

Pesticide Fact Sheet

Name of Chemical: Boscalid
Reason for Issuance: New Chemical
Date Issued: July 2003

Description of Chemical

Chemical Name:
3-pyridinecarboxamide, 2-chloro-N-(4'chloro[1,1'biphenyl]-2-yl)

Common Name: Boscalid (BAS 510)

Trade Names: Emerald, Endura, and Pristine

Chemical Class: Carboxamide aka anilide

EPA Chemical Code: 128008

Chemical Abstracts Service (CAS) Number: 188425-85-6

Year of Initial Registration: 2003

Pesticide Type: Fungicide

U.S. Producer: BASF

Use Pattern and Formulations

Boscalid is a fungicide consisting of two formulated end-use products for use on food crops. The wettable granule (WG) Endura Fungicide contains 70% active ingredient, and the wettable granule (WG) Pristine contains a mixture of boscalid (25.2% active) and pyraclostrobin (12.8% active). Endura™ is intended for use on beans, berries, bulb vegetables, canola, carrots, fruiting vegetables, grapes, lettuce, peanuts, pistachios, potatoes, stone fruit, strawberries, tree nuts, *Brassica* vegetables (subgroups 5A and 5B), cucurbit vegetables, mint, edible peas, certain root vegetables, and sunflower. Pristine™ is intended for use on berries, bulb vegetables, carrots, grapes, pistachios, stone fruit, strawberries, and tree nuts. Application is via multiple, foliar, broadcast sprays at a seasonal rate of ca 0.9-1.8 lbs ai/A, depending on crop and target disease. Typically, retreatment intervals are 1-3 weeks and minimum PHIs are 0-30 days.

There is also a formulated 70% wettable granule end-use product named Boscalid Turf Fungicide for use on golf course turfgrass. No other residential uses have been proposed.

Science Findings

Summary Science Statement

The Agency has completed its review of the product chemistry, toxicology, residue chemistry, occupational exposure, ecological effects and environmental fate data submitted in support of the registration of boscalid.

The toxicology data base for boscalid is adequate to support the requested field use registrations and tolerances. There is high confidence in the hazard endpoints and dose-response assessments conducted for this chemical.

Boscalid is classified as "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential". Therefore, a cancer risk assessment is not required.

The Agency has considered available information on boscalid's toxicity, potential use areas, fate properties, and application methods in characterizing ecological risks related to labeled use. Boscalid is persistent, it has low mobility in soil; however, boscalid may move to surface water through spraydrift and runoff of soil and suspended sediments. The degree of surface water contamination is mitigated by the relatively low seasonal application rates (2.1 lbs ai/acre/season) and its tendency to sorb to soil and sediment. The compound does not bioaccumulate appreciably in fish (BCF 35X-105X).

The fungicide is practically nontoxic to terrestrial animals and is moderately toxic to aquatic animals on an acute exposure basis. Boscalid acute risk quotients (RQs) do not exceed acute risk levels of concern and is not likely to pose an acute risk to animals at the maximum use rate. The RQ is not an absolute estimate of the likelihood, magnitude, or severity of risk. Inputs into this screening level assessment were designated to overestimate likely exposures and effects of boscalid. Given the slight exceedences of the RQs and the label limitations that will be imposed for boscalid, the Agency believes that potential ecological risks are low.

Physical/Chemical Properties

Physical and Chemical Properties for Technical Grade Active Ingredient

Requirement	Result
Color/Physical State	White powder (TGAI); White crystalline (PAI)
Odor	TGAI - faint smoky PAI - odorless
Stability	The test substance was found to be stable at RT and 54C for 14 days. The test substance was also found to be stable when exposed to metals like AI, & Fe, and to corresponding acetate ions.
Oxidation/Reduction	It reacts very weakly with potassium permanganate but does not react with iron, water or the fire extinguishing agent monoammonium phosphate (MAP). It is a very

	weak reducing agent.
Flammability	.Not applicable
Explodability	Non-explosive
Storage Stability	Not required for a TGAI. Accelerated storage at 54° C, in glass: day 0 - 98.16%, day 30 - 97.96.
Miscibility	.Not applicable
Corrosion Characteristics	The test substance is not expected to be corrosive to the commercial storage container
pH	5.5 at 23°C (1% solution)
Viscosity	.Not applicable
Melting Point/ Melting Range	143.4-143.6E C (TGAI); 142.8-143.8EC (PAI)
Density	1.394 g/cm^3 (TGAI); 1.381 g/cm^3 (PAI)
Dissociation Constant in Water	Test substance does not dissociate
Partition Coefficient (Octanol/Water)	log P o/w = 2.96; P o/w = 915 @ 21°C
Solubility:	PAI at 20°C in acetone (16-20 g/100 ml); acetonitrile (4-5 g/100ml); methanol (4-5 g/100 ml); ethylacetate (6.7-8 g/100 ml); dichloromethane (20-25 g/100 ml); toluene (2-2.5 g/100 ml); 1-octanol (<1 g/100 ml; water, 6 mg/L@20 C)
Vapor Pressure	7 x 10^{-9} hPa (PAI at 20°C); 2 x 10^{-8} hPa (PAI at 25°C)

Toxicological Characteristics:

Acute Toxicity Profile - Boscalid Technical

Test Material	GDLN	Study Type	MRID	Results	Tox Category
Technical	870.1100	Acute Oral - rat	45404814	LD_{50} > 5000 mg/kg	IV
Technical	870.1200	Acute Dermal - rat	45404815	LD_{50} > 2000 mg/kg	III
Technical	870.1300	Acute Inhalation	45404816	LC_{50} (M & F): > 6.7 mg/L	IV
Technical	870.2400	Primary Eye Irritation	45404817	Not irritating to the eye	IV

Technical	870.2500	Primary Dermal Irritation	45404818	Not irritating to the skin	IV

Technical	870.2600	Dermal Sensitization	45404819	Study unacceptable as challenge dose was inadequate	N/A

Toxicity Profile of Boscalid Technical.

Guideline No.	Study Type	Results
870.3100	90-Day oral toxicity rodents (rats)	**NOAEL**: 34/159 mg/kg/day (M/F) **LOAEL**: 137/395 mg/kg/day (M/F): M = increases in absolute and relative thyroid weights and increased incidence of thyroid hyperplasia as well as follicular epithelial hypertrophy; F = increases in absolute and relative thyroid weights.
870.3100	90-Day oral toxicity rodents (mice)	**NOAEL**: 197/2209 mg/kg/day (M/F) **LOAEL**: 788/2209 mg/kg/day (M/F): M = increased liver weights and increased incidence of marked fatty change in the liver; F = not attained
870.3150	90-Day oral toxicity in nonrodents (dogs)	**NOAEL**: 7.6/8.1 mg/kg/day (M/F) **LOAEL**: 78.1/81.7 mg/kg/day (M/F): M = increased alkaline phosphatase activity and hepatic weights; F = increased alkaline phosphatase activity and hepatic weights.
870.3200	21/28-Day dermal toxicity (rats)	**NOAEL**: 1000 mg/kg/day (HDT) **LOAEL**: >1000 mg/kg/day
870.3700	Prenatal developmental in rodents (rats)	**Maternal NOAEL**: 1000 mg/kg/day **Maternal LOAEL**: cannot be established **Developmental NOAEL**: 1000 mg/kg/day **Developmental LOAEL**: cannot be established
870.3700	Prenatal developmental in nonrodents (rabbit)	**Maternal NOAEL**: 300 mg/kg/day **Maternal LOAEL**: 1000 mg/kg/day based on abortions or early delivery. **Developmental NOAEL**: 300 mg/kg/day **Developmental LOAEL**: 1000 mg/kg/day based on abortions or early delivery.
870.3800	Reproduction and fertility effects (rat)	**Parental systemic NOAEL**:112.6/1180.8 mg/kg/day (M/F) **Parental systemic LOAEL**:1165.0/>1180.8

		mg/kg/day (M/F) decreased body weight and body weight gain (F_1) as well as hepatocyte degeneration F_0 and F_1) in males only. **Offspring systemic NOAEL**:11.2/115.8 mg/kg/day (M/F) **Offspring systemic LOAEL**:112.6/1180.8 mg/kg/day (M/F): decreased body weight for F_2 pups in males and females of both generations. **Reproductive NOAEL**:1165.0/1180.8 mg/kg/day (M/F) **Reproductive LOAEL**:>1165.0/1180.8 (M/F)
870.4100a	Chronic toxicity rodents (rat)	**NOAEL**: 21.9/30.0 mg/kg/day (M/F) **LOAEL**: 110.0/150.3 mg/kg/day (M/F): M = thyroid toxicity (weights and microscopic changes); F = thyroid toxicity (weights and microscopic changes). Thyroid follicular cell adenomas: M = 0/20, 0/20, 2/20,1/20; F = 0/20, 0/20, 1/20,0/20.
870.4100	Chronic toxicity dogs	**NOAEL**: 21.8/22.1mg/kg/day (M/F) **LOAEL**:57.4/58.3 mg/kg/day (M/F): M = elevated ALP activities and elevated hepatic weights; F = no effects
870.4200	Carcinogenicity rats	**NOAEL**: 23.0/29.7 mg/kg/day (M/F) **LOAEL**: 116.1/155.6 mg/kg/day (M/F): M = increased incidence of thyroid follicular cell hyperplasia and hypertrophy; F = decrease in body weight gain and increased incidence of thyroid follicular cell hyperplasia and hypertrophy. Thyroid follicular cell adenomas: M = 0/50, 0/50, 1/50, 4/50; F = 0/50, 1/50, 0/50, 3/50.
870.4200	Carcinogenicity mice	**NOAEL**:65/443 mg/kg/day (M/F) **LOAEL**: 331/1804 mg/kg/day (M/F): M = decreases in body weight and body weight gains; F = decreases in body weight and body weight gains. No evidence of carcinogenicity.
870.4300	Chronic feeding/Carcinogenicity rat	See 870.4100a and 870.4200.
870.5100	Gene Mutation bacterial reverse mutation assay	Negative without and with S-9 activation up to limit dose of 5000 µg/plate.
870.5300	*In vitro* mammalian cell forward gene mutation assay (CHO cells/HGPRT locus)	Negative without and with S-9 activation up to the limit of solubility of 25 µg/mL.
870.5375	*In vitro* mammalian cytogenetics assay in Chinese hamster V79 cells	Negative without and with S-9 activation up to 3500 µg/mL with precipitation showing at concentrations of 100 µg/mL and higher.

870.5395	Cytogenetics - mammalian erythrocyte micronucleus test in the mouse	Negative at doses up to 2000 mg/kg.
870.5500	*In vitro* unscheduled DNA synthesis (primary rat hepatocytes)	Negative response up to 50 µg/mL. Cytotoxicity at 100-500 µg/mL.
870.6200	Acute neurotoxicity screening battery (rat)	**NOAEL**:2000/1000 mg/kg/day (M/F) **LOAEL**: >2000/2000 mg/kg/day (M/F): F = piloerection
870.6200	Subchronic neurotoxicity screening battery (rat)	**NOAEL**:1050.0/1272.5 mg/kg/day (M/F) **LOAEL**: >1050.0/1272.5 mg/kg/day (M/F)
870.6300	Developmental neurotoxicity (rat)	**Maternal NOAEL:**1442 mg/kg/day **Maternal LOAEL:** >1442 mg/kg/day **Offspring NOAEL:** 14 mg/kg/day **Offspring LOAEL:** 147 mg/kg/day (decreased body weights on PND 4 and decreased body weight gain on PNDs 1-4)
870.7485	Metabolism and pharmacokinetics (rat)	Boscalid was readily absorbed and excreted following single oral 50 mg/kg; at single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion mainly by feces (80-98%). Biliary excretion 40-50% of fecal activity at 50 mg/kg, 10% at 500 mg/kg. Urine, about 16% at 50 mg/kg, 3-5% at 500 mg/kg. Absorption about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns similar by gender or radiolabel position. Metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with glucuronic acid or sulfate, or by conjugation of the parent with glutathione with cleavage to sulfate metabolites.
870.7600	Dermal Penetration (rat)	Maximum % absorption: 0.01 mg/cm^2 = 10.93 (24 hour exposure, 24 hour sacrifice) 0.10 mg/cm^2 = 3.76 (24 hour exposure, 24 hour sacrifice) 1.00 mg/cm^2 = 1.48 (10 hour exposure, 72 hour sacrifice)
none	SPECIAL STUDY: Hepatic enzyme induction (rat)	1. hypertrophy of zone III hepatocytes 2. >20% increase in liver weight 3. increase in CYP450 activity 4. slight to extensive microscopic SER proliferation 5. not a peroxisome proliferator

		6. enzymes in CYP450 subfamily not induced 7. no notable microscopic increase in size or number of peroxisomes CONCLUSION: inducer of total CYP450 activity
none	SPECIAL STUDY: Hormone and enzyme induction (rat)	1. slight (statistically significant) decrease in circulating T_3 and T_4 only in males 2. increase in circulating TSH levels both sexes 3. increase in all 3 liver microsomal glucuronyltransferases CONCLUSION: disruption of thyroid homoeostasis by decreasing circulating T_3 and T_4 and increasing TSH; likely the result of hepatic microsomal glucuronyltransferase induction
none	SPECIAL STUDY: Reversibility study (dietary): 4-week administration followed by 4 weeks recovery or 13 weeks recovery (rat)	4 weeks dosing: at 2500 and 15000 ppm: increase in TSH (68% and 87%); increase in absolute and relative thyroid weights, hypertrophy of thyroid follicular epithelial cells and diffuse follicular hyperplasia, increase in absolute and relative liver weights and centrilobular hypertrophy as well as liver portal fatty changes. 4 weeks dosing + 4 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. 4 weeks dosing + 13 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. CONCLUSION: induction of liver microsomal enzyme system resulting in increased glucuronidation of thyroxine, resulting in an increase in TSH secretion as a compensatory response of the physiological negative feedback system; increased TSH resulted in increased thyroid weight.

Summary of Toxicology Findings.

Boscalid has a low toxicity (toxicity categories III or IV for oral, dermal, inhalation, primary eye irritation and primary skin irritation). In a dermal sensitization study in guinea pigs, the study was unacceptable because the concentration used for the challenge was inadequate.

In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased

body weights and body weight gains (primarily in mice) and effects on the liver (increase in weights, changes in enzyme levels and histopathological changes) as well as on the thyroid (increase in weights and histopathological changes).

In a developmental toxicity study in rats, no developmental toxicity was observed in the fetuses at the highest dose tested (Limit Dose). No effects were noted in the dams in this study. In a developmental toxicity study in rabbits, an increased incidence of abortions or early delivery was observed at the Limit Dose. Since it could not be determined whether the abortions or early delivery were due to maternal toxicity or due to an effect on reproductive/developmental mechanisms, the LOAELs and NOAELs in this study for both maternal and developmental toxicity were considered to be the same. The does (maternal toxicity) and fetuses (developmental toxicity) were considered to be equally sensitive to the test material. This study does not indicate an increased susceptibility of fetuses, as compared to does. In a 2-generation reproduction study in rats, the NOAEL for parental toxicity was based on decreased body weight and body weight gain as well as hepatocyte degeneration. The NOAEL for offspring toxicity was based on decreased body weights and body weight gains for the pups. No reproductive toxicity was observed in this study at the highest dose tested. There was no evidence of susceptibility in the developmental rat study. There was evidence of qualitative (not quantitative) susceptibility in the developmental rabbit study as characterized by an increased incidence of abortions or early delivery at the highest dose tested. There was quantitative evidence of increased susceptibility in the two-generation reproduction study in rats, where decreases in body weights and body weight gains in male offspring were seen at a dose that was lower than the dose that induced parental/systemic toxicity. There was quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats, where decreases in pup body weights (PND 4) and body weight gains (PND 1-4) were seen in the absence of any maternal toxicity.

In a two-year chronic toxicity study and a two-year carcinogenicity study in male and female rats, the combined data showed that, for thyroid follicular cell adenomas, males had a significant increasing trend and significant differences in the pair-wise comparison of the highest dose group, when compared with controls. There was no treatment-related increase in thyroid follicular cell carcinomas. The increased incidence of the thyroid follicular cell adenomas exceeded the historical control mean and range. The increase in thyroid follicular cell adenomas appeared to be treatment-related in males. This was supported by thyroid hypertrophy and hyperplasia of follicular cells at the same dose as well as increased thyroid weights plus mechanistic data. Regarding females, combined data from the two rat studies indicated that there was an increasing trend for thyroid follicular cell adenomas which appeared to be treatment related. No carcinomas were observed in females. Boscalid is classified as, "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", according to the EPA *Draft Proposed Guidelines for Carcinogen Risk Assessment* (July 2, 1999).

Boscalid (BAS 510 F) was tested in five mutagenicity studies and was found to be negative in all of them.

In neither an acute nor a subchronic neurotoxicity study in rats was there evidence of a neurotoxic effect at the Limit Dose. In a developmental neurotoxicity study in rats, there were no neurotoxic effects observed at the Limit Dose. No neurotoxic observations were noted in any of the other studies in any species.

In metabolism and pharmacokinetic studies, Boscalid was readily absorbed and excreted following a single oral dose of 50 mg/kg. At single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion was mainly by feces (80-98%). Biliary excretion was 40-50% of fecal activity at 50 mg/kg and 10% at 500 mg/kg. Urinary content was about 16% at 50 mg/kg and 3-5% at 500 mg/kg. Absorption was about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns were similar by gender or radiolabel position. Metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with glucuronic acid or sulfate, or by conjugation of the parent with glutathione with cleavage to sulfate metabolites.

A dermal absorption study in rats is available. Doses used were 0.01, 0.10 and 1.0 mg/cm^2. The maximum percent absorptions were as follows: 0.01 = 10.93 (24 hour exposure, 24 hour sacrifice); 0.10 = 3.76 (24 hour exposure, 24 hour sacrifice); and 1.00 = 1.48 (10 hour exposure, 72 hour sacrifice). The total amount of absorption was 15% as represented by 11% being absorbed at 24 hours plus 4% found as bound residue on the skin.

Occupational and Residential Exposure and Risk Characterization.

All MOEs for the handlers performing agricultural crop uses were greater than the target of 100 at the baseline level (ranging from 460 to 31,000). All MOEs for the handlers performing golf course turfgrass uses were also greater than the target of 100 at the baseline level (ranging from 7,300 to 27,000).

The handler exposure estimates in this assessment are based on a central tendency estimate of unit exposure and an upper-percentile assumption for the application rate, and are assumed to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data (e.g., differences in use scenario and data confidence), and assumptions regarding that amount of chemical handled. The estimated exposures are believed to be reasonable high-end estimates based on observations from field studies and professional judgement.

The Agency uses the term “post-application” to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide. There are two recreational scenarios associated with boscalid that could lead to exposures for adults and children: 1.) golfing and 2.) picking their own fruit. These exposure durations are anticipated to be short-term (golfing) or acute (one day for picking fruit). Because “pick your own fruit” is considered a “one-time” event (duration <1 day) and oral studies indicated there were no toxicological endpoints appropriate to quantitate acute risk, this exposure scenario was not evaluated.

The boscalid label specifies that this product is intended for golf course use only, and not for use on residential turfgrass or turfgrass being grown for sale or other commercial use such as sod production. Although the label does not indicate that the product is applied by licenced or commercial applicators, it is acknowledged that the homeowner will not be applying the product to golf courses. Therefore, a risk assessment for residential handler exposure is not required.

FQPA CONSIDERATIONS

The special FQPA safety factor is reduced to 1X because the existing data indicate that there are no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity.

Conservative residue assumptions are used in the dietary risk assessments; there are no uses that will result in residential exposure except golf course and pick-your-own fruits; and the residue chemistry and environmental fate databases are relatively complete (evaluated by the risk assessment team). A 1X database factor is to be applied to all dietary and residential exposure endpoints as there are no data gaps. The Agency selected endpoints for chronic dietary exposure (all populations), incidental oral short- and intermediate-term residential only, dermal (all durations) and inhalation (all durations). As there were no toxic effects attributable to a single dose, an endpoint of concern was not identified to quantitate acute-dietary risk to the general population or to the subpopulation females 13-50 years old. Therefore, there is no acute reference dose (aRfD) or acute population-adjusted dose (aPAD). For all of the endpoints selected, liver and thyroid effects were chosen from the chronic toxicity study in rats, the carcinogenicity study in rats and the 1-year study in dogs. The NOAEL was 21.8 mg/kg/day. The uncertainty factor (UF) was 100. For the dermal route, the absorption rate was 15% relative to oral. For the inhalation route, the absorption rate was assumed to be 100%. The cPAD for the chronic dietary (all populations) exposure scenario = 0.218 mg/kg/day. The residential and occupational level of concern (LOC) is MOE = 100 for all routes (i.e., margins of exposure < 100 are of concern).

Exposure Scenario	Dose	Endpoint	Study/Effect
Acute dietary	No appropriate endpoint identified	none	not applicable
Chronic dietary (all populations)	NOAEL = 21.8 mg/kg/day	cRfD and cPAD = 0.218 mg/kg/day	Chronic rat, carcinogenicity rat and 1-year dog studies based on liver and thyroid effects.
Incidental oral (short- and intermediate-term residential only)	Oral NOAEL = 21.8 mg/kg/day	Target MOE = 100 (residential and occupational)	Chronic rat, carcinogenicity rat and 1-year dog studies based on liver and thyroid effects.
Dermal (all durations) Absorption: 15%	Oral NOAEL = 21.8 mg/kg/day	Target MOE = 100 (residential), 100 (occupational)	Chronic rat, carcinogenicity rat and 1-year dog studies based on liver and thyroid effects.
Inhalation (all durations) Absorption: 100%	Oral NOAEL = 21.8 mg/kg/day	Target MOE = 100 (residential), 100 (occupational)	Chronic rat, carcinogenicity rat and 1-year dog studies based on liver and thyroid effects.

Aggregate Exposure And Risk Characterization

Aggregate exposure risk assessments were performed for short term and chronic aggregate exposure. Short term and chronic aggregate exposures take into account dietary (food + drinking water) and residential exposures. Since the Agency does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, drinking water levels of comparison (DWLOCs) were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. The Agency uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate chronic DWLOCs, the dietary food estimates (from DEEM™) were subtracted from the chronic PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (adult male and US Population), 60 kg/2L (adult female), and 10kg/1L (infant & children).

As there were no toxic effects attributable to a single dose, an endpoint of concern was not identified to quantitate acute-dietary risk to the general population or to the subpopulation females 13-50 years old. Therefore, there is no acute reference dose (aRfD) or acute population-adjusted dose (aPAD) for the general population or females 13-50 years old. An acute aggregate risk assessment is not needed.

The chronic aggregate risk assessment takes into account average exposures estimates from dietary consumption of boscalid (food and drinking water) and residential uses. Since there are no chronic residential exposures associated with uses of boscalid, the chronic aggregate included food and drinking water only. The calculated chronic DWLOCs for chronic exposure to Boscalid in drinking water range from 1400 to 7000 µg/L (ppb). EECs generated are less than the calculated chronic DWLOCs . Therefore, the chronic aggregate risk associated with the proposed use of BAS 510 does not exceed the Agency's level of concern for the general U.S. population or any population subgroups.

Post application exposures from the sue oon golf couse is considered short term and applies to adults and youth. Although, a shourt term dermal risk assessment was conducted for the adult only, the adult MOEs are also considered representative for youths playing golf since the body surface area to weight ratios for adolescents do not vary significantly from those for adults. Since all endpoints are from the same study, exposure from different routes can be aggregated . The short term aggregate risk assessment takes into account average exposures from dietary consumption of boscalid (food and drinking water) and exposures from non-occupational sources (golf course). The calculated MOE from food and non-occupational exposure is 1200, and the calculated short term DWLOC is 6000 ppb. Compared to the surface water and ground waer EECs the short-term DWLOC is considerably larger and therefore the short term aggregate risk does not exceed the Agency's level of concern.
Cancer Assessment

The Agency classified Boscalid (BAS 510 F) as, "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", and, therefore, the quantification of human cancer risk is not recommended. The cancer classification was based on the following weight of evidence considerations. First, in male Wistar rats, there was a significant trend (but not pair wise comparison) for the combined thyroid adenomas and carcinomas. This trend was driven by the increase in adenomas. Second, in the female rats, there was only a borderline significant trend for thyroid adenomas (there were no carcinomas). Third, the mouse study was negative as were all of the mutagenic tests. Consistent with this weak evidence of carcinogenic effects, the Agency concluded that a dose-response assessment for cancer (either linear low-dose extrapolation or margin of exposure calculation) was not needed.

Ecological Effects/Environmental Fate Characteristics:

1. Environmental Fate Summary:

Boscalid is a slowly degradable compound with low mobility in most soils. The primary degradation

pathway is aerobic soil metabolism, which proceeds slowly and results in the formation of intermediates which are relatively rapidly transformed into CO_2 or bound soil residues. The majority of the apparent degradation of the compound is actually due to its transformation to bound residues. Degradates of the compound include 2-chloronicotinic acid (M510F47), 2-hydroxy-N-4'-chlorobiphenyl-2-yl)-nicotinamide (M510F49), and an unknown (M5100F50). Boscalid is hydrolytically stable and is photolytically stable on soil and in water. The compound is not transformed to any significant extent in either aerobic or anaerobic aquatic systems, but is relatively rapidly transferred (dissipation half-lives of <2 weeks) from the water phase to the sediment phase of sorbing to the sediment.

Boscalid has low mobility in most soils, as it tends to sorb to the organic matter. As such, it is likely to sorb to aquatic sediments. Data from batch equilibrium studies, when considered along with results from Tier 1 computer models and terrestrial field dissipation studies, indicate a low potential for leaching. A slightly higher potential for leaching exists for the compound in soils which are low in organic matter content, is as often the case with coarse-textured soils. There is a potential for Boscalid to reach surface water through spray drift when applied using ground spray (multiple crops) or aerial spray (canola). The potential for overland surface runoff of the compound in the water phase is low, although it may occur due to the aqueous solubility of the compound. However, because Boscalid is generally persistent under field conditions, over time the compound may be present in field runoff as a sorbed residue, and limited desorption of the bound parent compound from soil particles may occur in surface water bodies, particularly in soils with low organic matter content. The slow biodegradation of Boscalid in most soils will increase the potential for both groundwater and surface water contamination. However, the potential for groundwater contamination should be mitigated by the tendency of the compound to adsorb to surface soils, particularly those with relatively higher levels of organic matter. The potential for boscalid to leach in significant quantities or to reach surface water will be mitigated by the low application rate ($\leq$21b. a.i./A/season. Because boscalid does not biodegrade in aquatic systems, but does bind to sediments, the compound is expected to accumulate in the sediment phase of these environments. Results from Tier 1 models indicate that concentrations of Boscalid will be relatively low in groundwater and surface water, but that the compound will accumulate in surface water bodies. The boscalid degradate 2-chloronicotinic acid is very mobile in soil and is not expected to bind to aquatic sediments. However, the degradate is metabolized rapidly in aerobic soil, and is mineralize to CO_2 or tranformed to bound residues.

a. Hydrolysis

Boscalid is stable to hydrolysis at environmentally relevant pHs and temperature. Uniformly diphenyl ring-labeled [^{14}C]Boscalid, at 3 mg a.i./L (ppm) in sterile aqueous buffer solutions maintained at 25^{o}C for 30 days, was stable to hydrolysis at pH 5, 7 and 9. Based on the results obtained at 25^{o}C the parent compound is not expected to hydrolyze in the environment, rendering hydrolysis an insignificant fate process for boscalid.

b. Photolysis

Boscalid is stable to photolysis in water. Pyridine ring-labeled [3-^{14}C]Boscalid, at 3 µg a.i./mL (ppm), was stable to photolysis in sterile pH 5 (acetate) aqueous buffer solutions maintained at 22 $\pm$ 1^{o}C under continuous irradiation (xenon lamp) for 15 days. Based on the results of the study, photodegradation is not expected to be a significant route of dissipation for boscalid in the environment.

Boscalid is stable to photodegradation on soil. Pyridine ring-labeled [3-^{14}C]Boscalid, at 4.6 µg a.i./g soil (ppm), was stable to photodegradation on a standard (laboratory mix) German sandy loam soil (pH 7.3, organic carbon 1.9%) that was continuously irradiated (xenon lamp) while maintained at 22 $\pm$ 1°C and 40% of maximum water holding capacity for 15 days. Based on the results of the study, photodegradation is not expected to be a significant fate processor boscalid in the environment.

c. Metabolism

Boscalid is metabolized slowly in aerobic soils, while its degradate 2-chloronicotinic acid is metabolized rapidly in such soils. The biodegradation of boscalid (diphenyl and pyridine labels) was studied in multiple soils. The degradation of boscalid in aerobic soils was slow, with half-lives ranging from 96 to 578 days. It is noted, however, that the majority of the compound's apparent degradation is actually due to its transformation to bound residues rather than to actual degradation or complete mineralization of the compound.

Boscalid is degraded very slowly in anaerobic soils used on data obtained from two studies (diphenyl and pyridine labels) conducted using a standard (laboratory mix) German soil. Valid half-lives could not be determined in either study since the degradation of boscalid did not reach 50% of the applied by the end of the study periods (120 days). For assessment purposes, boscalid may be considered to be essentially stable to microbial degradation in anaerobic soils, as the disappearance of the parent compound was mainly due to bound residues, i.e., sorption, and no major degradates were detected.

d. Sediment/Water Systems

Boscalid is stable in anaerobic aquatic systems. Pyridine ring-labeled [^{14}C]Boscalid and uniformly diphenyl ring-labeled [^{14}C]Boscalid, at respective rates of 0.27 and 0.26 mg a.i./L, were metabolically stable in pond water/clay loam sediment systems (1:2 w:v;water pH 8.4; soil pH 7.3, organic matter 4.9%) from North Dakota, which were maintained at 20 $\pm$ 1°C under a nitrogen atmosphere for 361 days. In the water phase, [^{14}C]Boscalid decreased from 92.2-94.5% of the applied at day 0 to 50.9-53.1% by 7 days, and 9.6-14% by 35 days and 3.6 days and 3.6-4.6% by 361 days. In the sediment phase [^{14}C]Boscalid increased to a maximum of 59.1-61.9% by 35 days, then slowly decreased to 44.16-44.2% by 361 days. In total sediment:water system, [^{14}C]Boscalid decreased from 92.2-94.5% of the applied at day 0 to 49.7-51.8% at 179 days and 46.2-47.8% at 361 days. The calculated half-life (first-order linear) for the combined data was 385 days; DT50 (nonlinear) was 302-342 days. However, degradation was not observed, and the reported half-life is not true metabolic half-life. Disappearance of the parent was attributed to sediment binding. Residues partitioned to the soil with time; water:sediment and residue distribution were 1.2:1 at 7 days, 1:5 at 362 days; the vast majority of the bound residues were associated with the humin fraction of the soil organic matter. Volatiles were negligible.

Boscalid is stable in aerobic aquatic systems. Pyridine ring-labeled [^{14}C]Boscalid and uniformly diphenyl ring-labeled [^{14}C]boscalid, at 0.24 mg a.i./L, were metabolically stable in a water/German loamy sand sediment system (1:1.5, w:v; water pH 8.50, organic carbon 12.0-14.4 a pH in Ca $C1_2$ 6.8, organic carbon 0.8%) from a pond in Germany, an a water/German loam sediment system (1.2.1, w:v; water pH 8.10, organic carbon 8.6-15.2%; sediment pH in $CaC1_2$ 7.5, organic carbon 4.1-4.3%) from a pond-like area adjacent to a river in Germany, which were maintained at 20$\pm$ 2°C for 100 days. Aerobic conditions were maintained in the water layer f the

water/sediment systems, but the sediment layer remained anaerobic throughout the study. Total [^{14}C] residues of [^{14}C]Boscalid (both labels) gradually partitioned from the water layer to the loamy sand sediment with distribution ratios (water:sediment) of ca. 4:1 at day 1, 1:1 at 7-14 days, 1:2 at 29 days and 1:5 at 100 days but, in comparison, partitioned from the water layer to the loam sediment more rapidly, with distribution ratios of ca. 2:1 at day 1, 1:1 at 2 days, 1:2 at 7 days, 1:7 at 29 days and 1:15 at `100 days. No major degradates were detected in any of the systems. Non-extractable [^{14}C] residues in both sediments were 10.3-13.4% at 100 days. Volatiles were negligible. Boscalid was stable in all water/sediment systems, with dissipation of parent compound from the water layer to the sediment. Half-lives were not calculated for the total systems since degradation of the parent was negligible.

e. Mobility

Based on K_{oc} values and the McCall classification scheme (Swann et al., 1983), boscalid is expected to have low mobility in most soils and expected to bind to aquatic sediments. The adsorption of boscalid was assessed in two foreign soils (German standard soils; laboratory mixes), two U.S. soils and one Canadian soil at 22 $\pm$ 1°C in batch equilibrium studies using a 23-hour adsorption phase; desorption of the compound was assessed using a 16-hour desorption phase.

The boscalid degradate 2-chloronicotinic acid (M510F47) is expected to be very mobile in soil and is not expected to bind to aquatic sediments. The adsorption of the compound was assessed in three U.S. soils at 21°C in batch equilibrium studies using a 24-hour adsorption phase; desorption of the compound was assessed using a 16-hour desorption phase.

f. Field Dissipation

Based on terrestrial field dissipation studies, boscalid is generally persistent in the field, both in bare and cropped plots. The terrestrial field dissipation of boscalid was studied at several U.S. sites on various cropped and bare ground plots, and on bare ground plots in Canada.
The DT_{50}'s for dissipation of the parent compound from the surface solid for boscalid applied to bare ground plots (U.S. and Canada) ranged from 27 to 372 days (with the exception of a DT_{50} of 1 day which was of questionable validity due to data variability), and were generally greater than 100 days and frequently greater than 200 days. The residue carryover as a percentage of the total application range of 11.9-52.3% for the bare ground plots. The DT_{50}'s for dissipation of the parent compound from the surface soil for boscalid applied to cropped plots (U.S. only; turf, peach, almond) ranged from 44 to >360 days and were generally greater than 100 days. The residue carryover as a percentage of the total application was a range of 6.2-20.1% for the cropped plots. The maximum mean concentrations of the degradate M510F49 ranged from 0.01 mg/kg to 0.04 mg/kg across all studies. The maximum mean concentrations of the degradate M510F47 ranges from 0.003 mg/kg to 0.04 mg/kg across all studies.

g. Bioaccumulation

Boscalid is expected to accumulate in fish tissues at moderate levels, with greater accumulation in the nonedible tissue versus the edible tissue, but should depurate rapidly from the tissues when the fish are no longer exposed to the compound.

2. Ecological Risk Summary

a. Risk to Aquatic Organisms

Exposure to aquatic communities is expected to be limited due to the chemical's tendency to sorb to sediments. Boscalid is moderately toxic to aquatic animals; however based on estimated exposure concentrations, the proposed uses of boscalid are not likely to represent a threat to either acute or chronic ecological risk to freshwater fish and invertebrates or to estuarine/marine fish at a maximum proposed multiple application rates as high as six applications of 0.350 lbs. a.i./A. However, the acute risk level of concern for endangered species is exceeded for estuarine/marine invertebrates. While boscalid is not expected to adversely affect aquatic animals whose lives are primarily spent in open water, bottom-dwelling (benthic) fauna may be more likely to encounter boscalid based on the chemical's persistence and tendency to sorb to sediments. Modeling of benthic exposure, based on a closed farm pond scenario over a 36-year period, did not exceed the chronic risk level of concern for sediment-dwelling animals.

b. Risk to Avian Species (Acute/Chronic)

Boscalid is categorized as practically nontoxic to birds n both an acute and subacute exposure basis, no acute levels of concern (LOC) are exceeded for birds feeding on any of the modeled food items (short grass, tall grass, broadleaf plants insects and seeds). However, chronic exposure to boscalid at the proposed application rate for strawberries, i.e., 5 applications of 0.350 lbs a.i./A with a 7-day reapplication interval, results in the chronic risk level of concern being exceeded for birds feeding on short grasses (RQ=1.08). Exposure to boscalid on other avian food items (tall grasses, broadleaf plants/insects, and seeds) at this application rate did not result in any exceedance of either acute or chronic LOCs. Based on maximum estimated concentrations on short grass the chronic risk LOC would be exceeded for approximately 4 days; however, if mean foliar residues were used to estimate exposure, chronic avian LOCs would not have been exceeded since mean foliar residues are roughly half maximum exposure values.

c. Risk to Mammalians (Acute/Chronic)

Boscalid is practically nontoxic (LD_{50}>5,000 mg/kg) to rats on an acute exposure basis. Chronic toxicity data provided through a 2-generation rat production study indicated that decreased body weight and decreased body weight gains in F_2 males pups (NOAEC=100 ppm).

d. Risk to Plants

Ecological effects testing on a range of terrestrial and semi-aquatic plants revealed that the detrimental effects for all the test endpoints were less than 25% when compared with the pooled control. As a result, the EC_{25} was greater than 0.55 lb a.i./A. Therefore, RQ values have not been calculated for terrestrial and semi-aquatic plants and it is assumed that at rates less than or equal to 0.55 lbs/A, boscalid use does not represent a risk to plants.

DATA NEEDS

Label Restrictions

1. The Endura and Pristing labels must include a statement that use is prohibited on soybean, cowpea, field pea, and lupin; sugar beets, garden beets, turnips, and radishes.

2. Recropping (Plantback) Restrictions: The Endura™ and Pristine™ Fungicide labels must include a

statement that: "Crops with registered uses may be replanted at any time. All other crops grown for food or feed may be replanted after 14 days."

3. Maximum Seasonal Use Rate: As a precautionary measure, the Endura™ and Pristine™ Fungicide labels must include a statement to the effect that, if ever both these formulated products should be applied interchangeably to the same crop (i.e., same plants) during the growing of that crop, the total amount of ai/A applied to that crop must not exceed that allowed had only one of these formulated products been used (i.e., ca 0.9-1.8 lbs ai/A total per season, depending on the specific crop).

There are also several **conditions of registration** associated with the granting of these tolerances:

! Conditions of Registration

860 Series - Residue Chemistry
- Completion of Agency method validations
- Radiovalidation data demonstrating extraction efficiency of methods
- Storage stability - final plant report and data for grape juice and tomato paste
- Additional field trials for mustard greens, cucumbers and sunflower seed
- Field rotational crop data for best and turnip tops, spinach, and celery

Environmental Fate and Effects

Data Gap

1. Aquatic toxicity tests using fish and invertebrates were classified as supplemental since water quality parameters did not adherer to standards recommended by the Agency. If the registrant can demonstrate that pH, water hardness and the use of dechlorinated tap water do not affect the toxicity of boscalid and if it can be demonstrated that mean measured concentrations accurately reflect the amount of chemical in solution, these studies can be upgraded to core.

2. Submission of a freshwater invertebrate life cycle study - non of the required data are provided on growth (length and weight) of Daphnia magna. If registrant has these data, they should provide for review, otherwise the Agency recommends that the study be repeated.

3. Submission of the toxicity data must be provided for freshwater mollusc such as *Corbicula spp.*, given the persistence of boscalid and its tendency to partition on to sediments.

Label Language:

Surface Water Advisory:

"This product may contaminate water through drift spray in wind. This product has a potential for runoff according to the pesticide's "mean" soil partition coefficient (15 mgL/g^2) for several months or more after application. Poorly draining soils and soils with shallow water tables are more prone to produce runoff that contains this product. A level, well maintained vegetative buffer strip between areas to which this product is applied and surface water features such as ponds, streams, and springs will reduce the potential for contamination of water from rainfall-runoff. Runoff of this product will be reduced by avoiding applications when rainfall is forecasted to occur within 48 hours."

Contact person at USEPA

Mailing address

Cynthia Giles-Parker
Product Manager (22)
Environmental Protection Agency
Office of Pesticide Programs
Registration Division (7505C)
Fungicide Branch
1200 Pennsylvania Avenue NW
Washington, D.C. 20460

Office location and telephone number:

Room 249, Crystal Mall #2
1921 Jefferson Davis Highway
Arlington, VA 22202
703-305-7740

DISCLAIMER: The information in this Pesticide Fact Sheet is for information only and is not to be used to satisfy data requirements for pesticide registration. The information is believed to be accurate as of the date on the document.

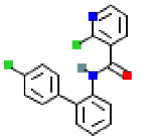
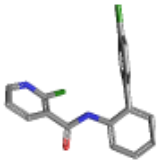
Attachment B

PubChem File

PubChem

COMPOUND SUMMARY

Boscalid

PubChem CID	213013
Structure	 2D  3D Find Similar Structures
Chemical Safety	 Environmental Hazard Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula	$C_{18}H_{12}Cl_2N_2O$
Synonyms	Boscalid 188425-85-6 Nicobifen Endura Emerald More...
Molecular Weight	343.2
Dates	Modify 2023-05-05 Create 2005-08-09

Boscalid is a pyridinecarboxamide obtained by formal condensation of the carboxy group of 2-chloronicotinic acid with the amino group of 4'-chlorobiphenyl-2-amine. A fungicide active against a broad range of fungal pathogens including Botrytis spp., Alternaria spp. and Sclerotinia spp. for use on a wide range of crops including fruit, vegetables and ornamentals. It has a role as an EC 1.3.5.1 [succinate dehydrogenase (quinone)] inhibitor, an environmental contaminant, a xenobiotic and an antifungal agrochemical. It is a member of biphenyls, a pyridinecarboxamide, a member of monochlorobenzenes and an anilide fungicide. It is functionally related to a nicotinic acid.

▸ ChEBI

Boscalid is a fungicide developed by BASF and launched in 2003 for use on food crops. It works as a **succinate** dehydrogenase inhibitor to kill fungal target organisms. It is practically nontoxic to terrestrial animals and is moderately toxic to aquatic animals on an acute exposure basis. In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased body weights and body weight gains (primarily in mice) and effects on the liver (increase in weights, changes in enzyme levels and histopathological changes) as well as on the thyroid (increase in weights and histopathological changes). In a developmental toxicity study in rats, no developmental toxicity was observed in the fetuses at the highest dose tested. Boscalid is classified as, suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential, according to the EPA.

- **Toxin and Toxin Target Database (T3DB)**

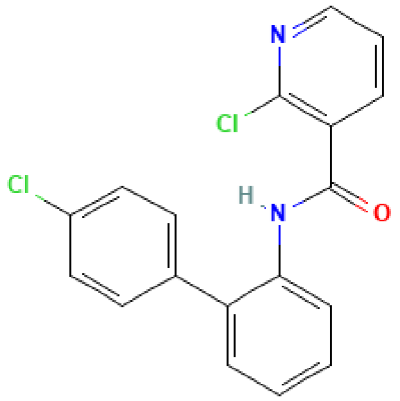
Boscalid has been investigated for the treatment of OSDI, Glaucoma, Staining, Schirmers, and Disease Severity, among others.

- **DrugBank**

1 Structures

1.1 2D Structure

Chemical Structure Depiction



PubChem

1.2 3D Conformer

PubChem

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

2-chloro-*N*-[2-(4-chlorophenyl)phenyl]pyridine-3-carboxamide

Computed by Lexichem TK 2.7.0 (PubChem release 2021.05.07)

PubChem

2.1.2 InChI

InChI=1S/C18H12Cl2N2O/c19-13-9-7-12(8-10-13)14-4-1-2-6-16(14)22-18(23)15-5-3-11-21-17(15)20/h1-11H,(H,22,23)

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.3 InChIKey

WYEMLYFITZORAB-UHFFFAOYSA-N

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.4 Canonical SMILES

C1=CC=C(C(=C1)C2=CC=C(C=C2)Cl)NC(=O)C3=C(N=CC=C3)Cl

Computed by OEChem 2.3.0 (PubChem release 2021.05.07)

PubChem

2.2 Molecular Formula

C18H12Cl2N2O

Wikipedia; PubChem

2.3 Other Identifiers

2.3.1 CAS

188425-85-6

- CAS Common Chemistry; ChemIDplus; DrugBank; EPA DSSTox; European Chemicals Agency (ECHA); FDA Global Substance Registration System (GSRS); Hazardous Substances Data Bank (HSDB)

2.3.2 European Community (EC) Number

606-143-0

- European Chemicals Agency (ECHA)

2.3.3 UNII

32MS8ZRD1V

- FDA Global Substance Registration System (GSRS)

2.3.4 DSSTox Substance ID

DTXSID6034392

- EPA DSSTox

2.3.5 Nikkaji Number

J1.989.940C

- Japan Chemical Substance Dictionary (Nikkaji)

2.3.6 Wikipedia

Boscalid

- Wikipedia

Emerald

- Wikipedia

2.3.7 Wikidata

Q894358

Wikidata

2.3.8 Metabolomics Workbench ID

153713

Metabolomics Workbench

2.4 Synonyms

2.4.1 MeSH Entry Terms

2-chloro-N-(4-chlorobiphenyl-2-yl)nicotinamide
boscalid

Medical Subject Headings (MeSH)

2.4.2 Depositor-Supplied Synonyms

Boscalid	32MS8ZRD1V	2-CHLORO-N-(4'-CHLORO(1,1'-BIPHENYL)-2-YL)-3-PYRIDINECARBOXAMIDE
188425-85-6	DTXSID6034392	3-Pyridinecarboxamide, 2-chloro-N-(4'-chloro(1,1'-biphenyl)-2-yl)-
Nicobifen	BAS 510 F	HSDB 7499
Endura	CHEBI:81822	BOSCALID [HSDB]
Emerald	NCGC00163735-04	EMERALD [INCI]
2-Chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide	Anilide	BOSCALID [MI]
Boscalid [ISO]	Cantus	SCHEMBL18517
2-chloro-N-(4'-chlorobiphenyl-2-yl)nicotinamide	C18H12Cl2N2O	CHEMBL1076544
2-chloro-N-[2-(4-chlorophenyl)phenyl]pyridine-3-carboxamide	2-chloro-N-{4'-chloro-[1,1'-biphenyl]-2-yl}pyridine-3-carboxamide	DTXCID4014392
3-Pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)-	BAS 510F	AMY22452
Bas 510	UNII-32MS8ZRD1V	ZINC3612929
Bas-510	2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide	Tox21_400045

PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	343.2	Computed by PubChem 2.1 (PubChem release 2021.05.07)
XLogP3-AA	4.9	Computed by XLogP3 3.0 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	1	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Rotatable Bond Count	3	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Exact Mass	342.0326684	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Monoisotopic Mass	342.0326684	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	42 Å^2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Heavy Atom Count	23	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	399	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.05.07)

PubChem

3.2 Experimental Properties

3.2.1 Physical Description

White solid; [Merck Index] White powder; [MSDSonline]

Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

3.2.2 Color/Form

White crystalline

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.3 Odor

Odorless

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.4 Melting Point

142.8 to 143.8 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.5 Solubility

In water, 4.6 mg/L at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

Solubility in n-heptane, <10 g/L, 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

Solubility in acetone, 16-20 g/100 mL; acetonitrile, 4-5 g/100 mL; methanol, 4-5 g/100 mL; ethylacetate, 6.7-9 g/100mL; dichloromethane, 20-25 g/100 mL; toluene, 2-2.5 g/100 mL; 1-octanol, <1 g/100 mL, all at 20 °C

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.6 Density

1.381 at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.7 Vapor Pressure

0.00000001 [mmHg]

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

7.2X10-4 mPa /5.4X10-10 mm Hg/ at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.8 LogP

log Kow = 2.96

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.9 Henry's Law Constant

Henry's Law constant = 5.178X10-5 Pa- cu m/mol /5.3X10-11 atm-cu m/mol/ at 25 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.10 Stability/Shelf Life

Stable under recommended storage conditions.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ Hazardous Substances Data Bank (HSDB)

3.2.11 pH

pH = 5.5 at 23 °C (1% solution)

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.12 Ionization Efficiency

Ionization mode	Positive
logIE	2.55
pH	2.7
Instrument	Agilent XCT

Ion source	Electrospray ionization
Additive	formic acid (5.3nM)
Organic modifier	MeCN (80%)
Reference	DOI:10.1038/s41598-020-62573-z

Kruve Lab, Ionization & Mass Spectrometry, Stockholm University

3.2.13 Dissociation Constants

Does not dissociate

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

3.2.14 Collision Cross Section

171.67 Å^2 [M+H]$^+$ [CCS Type: TW]

https://pubs.acs.org/doi/abs/10.1021/acs.analchem.7b00741

CCSbase

178.57 Å^2 [M-H]$^-$

175.28 Å^2 [M+H]$^+$

179.04 Å^2 [M+Na]$^+$

S61 | UJICCSLIB | Collision Cross Section (CCS) Library from UJI | DOI:10.5281/zenodo.3549476

NORMAN Suspect List Exchange

3.2.15 Other Experimental Properties

White powder; faintly smoky odor; mp: 143.3 to 143.6 °C; density: 1.394 g/cu cm /Technical grade/

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

Stable to hydrolysis at pH 4, 5, 7 and 9; stable to aqueous photolysis

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

Hazardous Substances Data Bank (HSDB)

3.2.16 Chemical Classes

Pesticides -> Fungicides

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

4 Spectral Information

4.1 Mass Spectrometry

4.1.1 GC-MS

Showing 2 of 3 View More

NIST Number	366503
Library	Main library
Total Peaks	166
m/z Top Peak	140
m/z 2nd Highest	112
m/z 3rd Highest	142
Thumbnail	

NIST Mass Spectrometry Data Center

Source of Spectrum	Prof. L. Mondello (Chromaleont s.r.l./Univ. Messina, Italy)
Source of Sample	Sigma-Aldrich Cat. #33875
Copyright	Copyright © 2016-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

4.1.2 MS-MS

Showing 2 of 6 View More

Spectra ID	2226978
Ionization Mode	Positive
SPLASH	splash10-00di-0090000000-cc17078aea1a98911337
Top 5 Peaks	271.0862 100 272.0933 84.48 243.0908 26.13 254.0823 16.82 139.9887 15.92
Thumbnail	

Human Metabolome Database (HMDB)

Spectra ID	2231680
Ionization Mode	Positive
SPLASH	splash10-0006-0049000000-8426425d727d94705a43
Top 5 Peaks	341.0229 100 228.0225 78.38 343.0244 62.96
Thumbnail	

Human Metabolome Database (HMDB)

4.1.3 LC-MS

Showing 2 of 46 View More

Accession ID	MSBNK-Athens_Univ-AU232601
Authors	Nikiforos Alygizakis, Katerina Galani, Nikolaos Thomaidis, University of Athens
Instrument	Bruker maXis Impact
Instrument Type	LC-ESI-QTOF
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	10 eV
Fragmentation Mode	CID

Column Name	Acclaim RSLC C18 2.2um, 2.1x100mm, Thermo
Retention Time	9.441 min
Precursor m/z	343.0399
Precursor Adduct	[M+H]+
Top 5 Peaks	343.04 999 345.0367 506 344.0432 155 307.0627 42 139.9887 35
SPLASH	splash10-0006-0009000000-591e6e2226a81639a618
Thumbnail	
License	CC BY

MassBank Europe

Accession ID	MSBNK-Athens_Univ-AU232602
Authors	Nikiforos Alygizakis, Katerina Galani, Nikolaos Thomaidis, University of Athens
Instrument	Bruker maXis Impact
Instrument Type	LC-ESI-QTOF
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	20 eV
Fragmentation Mode	CID

Column Name	Acclaim RSLC C18 2.2um, 2.1x100mm, Thermo
Retention Time	9.463 min
Precursor m/z	343.0399
Precursor Adduct	[M+H]+
Top 5 Peaks	307.0632 999 343.04 545 345.0364 323 139.9886 313 309.0603 201
SPLASH	splash10-0a4i-0109000000-0ecd56268ec733edc02c
Thumbnail	
License	CC BY

MassBank Europe

4.1.4 Other MS

Showing 2 of 3 View More

MoNA ID	CCMSLIB00001058945
MS Category	Experimental
MS Type	Other
MS Level	MS2
Precursor Type	[M+H]+
Precursor m/z	369.217

Instrument	Maxis HD qTOF
Ionization Mode	positive
Top 5 Peaks	149.060333 100 133.066055 39.95 119.060516 13.07 91.054398 10.56 105.070152 9.59
SPLASH	splash10-0002-0900000000-e7af1cb312c23ffb73fb
Thumbnail	

MassBank of North America (MoNA)

MoNA ID	CCMSLIB00001058753
MS Category	Experimental
MS Type	Other
MS Level	MS2
Precursor Type	[M+Na]+
Precursor m/z	391.199
Instrument	Q-Exactive Plus Orbitrap Res 14k
Ionization Mode	positive
Top 5 Peaks	241.130539 100 72.081207 75.30 219.149689 28.13 391.201233 17.69

	335.138245 12.67
SPLASH	splash10-006x-5192000000-1b8f299a4832762a05a6
Thumbnail	

▸ MassBank of North America (MoNA)

5 Related Records

5.1 Related Compounds with Annotation

PubChem

5.2 Related Compounds

Same Connectivity	6 Records
Same Parent, Connectivity	14 Records
Same Parent, Exact	9 Records
Mixtures, Components, and Neutralized Forms	56 Records
Similar Compounds	411 Records
Similar Conformers	1,938 Records

PubChem

5.3 Substances

5.3.1 Related Substances

All	196 Records
Same	125 Records

Mixture	71 Records

PubChem

5.3.2 Substances by Category

PubChem

5.4 Entrez Crosslinks

PubMed	45 Records
Taxonomy	4 Records
Gene	352 Records

PubChem

5.5 NCBI LinkOut

NCBI

6 Chemical Vendors

PubChem

7 Drug and Medication Information

7.1 FDA National Drug Code Directory

- National Drug Code (NDC) Directory

BOSCALID is an active ingredient in the product EMERALD.

- National Drug Code (NDC) Directory

7.2 Clinical Trials

7.2.1 ClinicalTrials.gov

- ClinicalTrials.gov

8 Agrochemical Information

8.1 Agrochemical Category

Fungicide

- EPA Pesticide Ecotoxicity Database

Pesticide active substances

- EU Pesticides Database

Fungicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | ***DOI:10.5281/zenodo.3862688***

- NORMAN Suspect List Exchange

8.2 Agrochemical Transformations

Boscalid has known environmental transformation products that include M510M47, M510F49, Boscalid metabolite 1, M510F08, and M510F50.

S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 | ***DOI:10.5281/zenodo.3544759***

- NORMAN Suspect List Exchange

8.3 EU Pesticides Data

Active Substance	boscalid (formerly nicobifen)
Status	Date of Approval: 01/08/2008 Expiration of Approval: 31/07/2023 [Reg. (EC) No 1107/2009]
Legislation	Reg. (EU) 2022/708, 08/44/EC, Reg. (EU) 2018/917, Reg. (EU) 2019/707, Reg. (EU) 2020/869, Reg. (EU) 2021/745, Reg. (EU) No 540/2011
ADI	0.04 mg/kg bw/day [08/44/EC]
AOEL	0.1 mg/kg bw/day [08/44/EC]

- EU Pesticides Database

8.4 USDA Pesticide Data Program

Pesticide	Boscalid
Apple Juice	EPA tolerance level: 3.0 [ppm]
Blueberries, Cultivated,	EPA tolerance level: 13.0 [ppm]
Bananas	EPA tolerance level: 0.40 [ppm] (Import Tolerance)
Broccoli	EPA tolerance level: 6.0 [ppm]

Blueberries, Frozen	EPA tolerance level: 13.0 [ppm]
Cauliflower	EPA tolerance level: 6.0 [ppm]
Cantaloupe	EPA tolerance level: 3.0 [ppm]
Carrots	EPA tolerance level: 2.0 [ppm]
Eggplant	EPA tolerance level: 3.0 [ppm]
Green Beans	EPA tolerance level: 5.0 [ppm]
Collard Greens	EPA tolerance level: 60 [ppm]
Kiwi Fruit	EPA tolerance level: NT
Orange Juice	EPA tolerance level: 2.0 [ppm]
Sweet Bell Peppers	EPA tolerance level: 3.0 [ppm]
Radishes	EPA tolerance level: 2.0 [ppm]
Summer Squash	EPA tolerance level: 3.0 [ppm]
Tangerines	EPA tolerance level: 2.0 [ppm]
Tomato Paste	EPA tolerance level: 3.0 [ppm]
Winter Squash	EPA tolerance level: 3.0 [ppm]

▸ USDA Pesticide Data Program

9 Minerals

Name	EMERALD

Athena Minerals

10 Pharmacology and Biochemistry

10.1 Absorption, Distribution and Excretion

Dermal Penetration (rat). Maximum % absorption: 0.01 mg/sq cm = 10.93 (24 hour exposure, 24 hour sacrifice) 0.10 mg/sq cm = 3.76 (24 hour exposure, 24 hour sacrifice) 1.00 mg/sq cm = 1.48 (10 hour exposure, 72 hour sacrifice /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.7 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

In the rat, Boscalid was readily absorbed and excreted following single oral 50 mg/kg; at single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion mainly by feces (80-98%). Biliary excretion 40- 50% of fecal activity at 50 mg/kg, 10% at 500 mg/kg. Urine, about 16% at 50 mg/kg, 3-5% at 500 mg/kg. Absorption about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns similar by gender or radiolabel position. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.7 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

10.2 Metabolism/Metabolites

Three ... groups of Wistar rats were treated and sampled ... for qualitative analyses of metabolites. ... Metabolites were separated by HPLC. Primary identification was by mass spectrometry (MS). ... The most important metabolites were **hydroxyl** or O-glucuronide metabolites on the diphenyl ring (usually para to the amide **nitrogen**), and S-glucuronide conjugation products displacing the **chlorine** on the **pyridine** ring of the parent compound. The **sulfur** originated from **glutathione** (**GSH**) addition to the ring. **GSH** was often cleaved to **cysteine** in bile or feces, or further degraded in feces to a **thiol**, which in turn was sometimes conjugated as a glucuronide). Tissue residues (liver, kidney, and plasma) were scant ... Some parent BAS 510 F was found in kidneys and plasma. Thus BAS 510 F was effectively metabolized and efficiently excreted.

California Environmental Protection Agency/Department of Pesticide Regulation; Summary of Toxicological Data for BAS 510 F, Chemical Code No.5790 p.9 (May 2, 2002, Revised May 20, 2013). Available from, as of June 15, 2016: ***https://www.cdpr.ca.gov/docs/risk/toxsums/toxsumlist.htm***

▸ **Hazardous Substances Data Bank (HSDB)**

/In the rat,/ metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with **glucuronic acid** or **sulfate**, or by conjugation of the parent with **glutathione** with cleavage to **sulfate** metabolites. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.7 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

10.3 Biological Half-Life

In the rat, the predominant route of excretion of BAS 510 F is fecal with urinary excretion being minor. The half-life of BAS 510 F is less than 24 hours.

BASF Submission to EPA; Request for consideration of a tolerances for residues of Boscalid (BAS 510F). EPA-HQ-OPP-2005-0145-004 (EPA Docket) (2005)

▸ **Hazardous Substances Data Bank (HSDB)**

10.4 Transformations

- NORMAN Suspect List Exchange

11 Use and Manufacturing

11.1 Uses

EPA CPDat Chemical and Product Categories

*The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products, Scientific Data, volume 5, Article number: 180125 (2018), **DOI:10.1038/sdata.2018.125***

▸ **EPA Chemical and Products Database (CPDat)**

Sources/Uses

Used as a broad spectrum carboxamide fungicide to control diseases in turf, field, row, orchard, and vineyard crops; [Merck Index]

Merck Index - O'Neil MJ, Heckelman PE, Dobbelaar PH, Roman KJ (eds). The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 15th Ed. Cambridge, UK: The Royal Society of Chemistry, 2013.

▸ **Haz-Map, Information on Hazardous Chemicals and Occupational Diseases**

Industrial Processes with risk of exposure

Farming (Pesticides) [Category: Industry]

▸ **Haz-Map, Information on Hazardous Chemicals and Occupational Diseases**

For boscalid (USEPA/OPP Pesticide Code: 128008) ACTIVE products with label matches. /SRP: Registered for use in the U.S. but approved pesticide uses may change periodically and so federal, state and local authorities must be consulted for currently approved uses./

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 21, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

▸ **Hazardous Substances Data Bank (HSDB)**

Fungicide, plant health product, seed treatment/protectant.

Crop Protection Handbook Volume 100, Meister Media Worldwide, Willoughby, OH 2014, p. 141

Hazardous Substances Data Bank (HSDB)

This is a man-made compound that is used as a pesticide.

Toxin and Toxin Target Database (T3DB)

11.1.1 Use Classification

Agrochemicals -> Pesticides

EU Pesticides Database

Fungicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | DOI:10.5281/zenodo.3862688

NORMAN Suspect List Exchange

Environmental transformation -> Pesticides (parent, predecessor)

S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 | DOI:10.5281/zenodo.3544759

NORMAN Suspect List Exchange

11.1.2 Household Products

Household & Commercial/Institutional Products

Information on 2 consumer products that contain Boscalid in the following categories is provided:

- Landscaping/Yard
- Pesticides

Consumer Product Information Database (CPID)

11.2 Methods of Manufacturing

Boscalid can be synthesized by reaction of 2-amino-4'-chlorobiphenyl in aqueous xylene with 2-chloro-3-pyridinecarbonyl chloride.

Muller F et al; Fungicides, Agricultural, 2. Individual Fungicides. Ullmann's Encyclopedia of Industrial Chemistry 7th ed. (1999-2016). NY, NY: John Wiley & Sons. Online Posting Date: October 15, 2011

Hazardous Substances Data Bank (HSDB)

2-Halopyridinecarboxamides of primary aromaticity in /the/ ortho-position-substituted monoamine, were prepared by reacting 2-halopyridinecarbonyl chloride with the corresponding aromatic monoamine in a solvent mixture containing water and greater than 1 solvent non-mixable with water; whereby the reaction mixture comprises a base in a quantity of 0-<10 mol% based on the 2-halopyridinecarbonyl chloride. Thus a mixture of water and 2-amino-4'-chlorobiphenyl in xylene was heated at 65 °C under stirring followed by /the/ addition of 2-chloro-3-pyridinecarbonyl chloride and stirring for 10 minutes at 95 °C to give 93% /boscalid/.

Mayer H et al; PCT Int Appl, WO 2003037868, BASF Aktiengesellschaft, Germany, 16pp. (2003)

Hazardous Substances Data Bank (HSDB)

Preparation: K. Eicken et al., European Patent Office patent 545099; eidem, United States of America patent 5589493 (1993, 1996 both to BASF).

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 237

Hazardous Substances Data Bank (HSDB)

11.3 Formulations/Preparations

Endura Fungicide (BASF Corporation): Active ingredient: Boscalid 70.0%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

Emerald Fungicide (BASF Corporation): Active ingredient: Boscalid 70.0%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

Boscalid Technical (BASF Corporation): Active ingredient: Boscalid 99.0%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

Pristine Fungicide (BASF Corporation): Active ingredient: Pyraclostrobin 12.8%; Boscalid 25.2%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

For more Formulations/Preparations (Complete) data for BOSCALID (14 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

11.4 General Manufacturing Information

The WHO Recommended Classification of Pesticides by Hazard identifies boscalid as unlikely to present an acute hazard in normal use; Main Use: fungicide, other than for seed treatment.

WHO International Programme on Chemical Safety; The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009 p.39 (2010)

Hazardous Substances Data Bank (HSDB)

12 Identification

12.1 Analytic Laboratory Methods

Sudden infant death syndrome (SIDS) and sudden intrauterine unexpected death syndrome (SIUDS) are an unresolved teaser in the social-medical and health setting of modern medicine and are the result of multifactorial interactions. Recently, prenatal exposure to environmental contaminants has been associated with negative pregnancy outcomes, and verification of their presence in fetal and newborn tissues is of crucial importance. A gas chromatography-tandem mass spectrometry (MS/MS) method, using a triple quadrupole analyzer, is proposed to assess the presence of 20 organochlorine pesticides, two organophosphate pesticides, one **carbamate** (boscalid), and a **phenol** (**bisphenol A**) in human brain tissues. Samples were collected during autopsies of infants and fetuses that died suddenly without any evident cause. The method involves a liquid-solid extraction using **n-hexane** as the extraction solvent. The extracts were purified with **Florisil** cartridges prior to the final determination. Recovery experiments using lamb brain spiked at three different concentrations in the range of 1-50 ng/g were performed, with recoveries ranging from 79 to 106%. Intraday and interday repeatability were evaluated, and relative standard deviations lower than 10% and 18%, respectively, were obtained. The selectivity and sensitivity achieved in multiple reaction monitoring mode allowed us to achieve quantification and confirmation in a real matrix at levels as low as 0.2-0.6 ng/g. Two MS/MS transitions were acquired for each analyte, using the Q/q ratio as the confirmatory parameter. This method was applied to the analysis of 14 cerebral cortex samples (ten SIUDS and four SIDS cases), and confirmed the presence of several selected compounds.

PMID:25665709

Termopoli V et al; Anal Bioanal Chem 407 (9): 2463-72 (2015)

Hazardous Substances Data Bank (HSDB)

Boscalid is a new-generation fungicide that has been detected in several bee matrices. The objective of this work was to characterize boscalid metabolites in honeybees based on in vivo experimentation, and next to verify the presence of these metabolites into honeybees from colonies presenting troubles. A methodology based on complementary mass spectrometric tools, namely ultra-high performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-QToF) or triple quadrupole mass spectrometry (UHPLC-QqQ) was implemented. Honeybees were sprayed with boscalid, at field rate (to induce the metabolization process) and the parent compound with its generated metabolites were then extracted using modified EU-QuEChERS method. The mass characteristics including exact mass, isotopic profile and mass fragments allowed assuming the structure of several metabolites. Some of them were unambiguously identified by comparison with synthesized analytical standards. The metabolites were resulted from hydroxylation and dechlorination of the parent compound as well as the substitution of a **chlorine** atom with a **hydroxyl** group. The metabolites were then quantified in bee samples collected from various beehives located in France.Boscalid and three of its metabolites were present in some samples at a level ranged between 0.2 and 36.3 ng/g.

PMID:27179242

Jabot C et al; Chemosphere 156: 245-51 (2016)

Hazardous Substances Data Bank (HSDB)

Analytical method. In plants the parent residue is extracted using an aqueous/organic solvent mixture followed by liquid/liquid partitioning and a column clean up. Quantitation is by gas chromatography using mass spectrometry (GC/MS). In livestock the residues are extracted with **methanol**. The extract is treated with enzymes in order to release the conjugated **glucuronic acid** metabolite. The residues are then isolated by liquid/liquid partition followed by column chromatography. The hydroxylated metabolite is acetylated followed by a column clean-up. The parent and acetylated metabolite are quantitated by gas chromatography with electron capture detection.

BASF Submission to EPA; Request for consideration of a tolerances for residues of Boscalid (BAS 510F). EPA-HQ-OPP-2005-0145-004 (EPA Docket) (2005)

Hazardous Substances Data Bank (HSDB)

13 Safety and Hazards

13.1 Hazards Identification

13.1.1 GHS Classification

Showing 1 of 2 View More

Pictogram(s)	 Environmental Hazard
GHS Hazard Statements	H411 (100%): Toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
Precautionary Statement Codes	P273, P391, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)
ECHA C&L Notifications Summary	*Aggregated GHS information provided by 288 companies from 3 notifications to the ECHA C&L Inventory.* *Reported as not meeting GHS hazard criteria by 3 of 288 companies. For more detailed information, please visit ECHA C&L website.* *Of the 2 notification(s) provided by 285 of 288 companies with hazard statement code(s).* *Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.*

▸ European Chemicals Agency (ECHA)

13.1.2 Hazard Classes and Categories

Aquatic Chronic 2 (100%)

▸ European Chemicals Agency (ECHA)

13.1.3 Hazards Summary

In high-dose animal studies, causes changes in thyroid and liver; [RTECS] Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential. Practically nontoxic to terrestrial animals and moderately toxic to aquatic animals for acute exposures; Ecological risks are low; Slowly degradable with low mobility in most soils; Exposure of aquatic animals is limited by chemical's tendency to sorb to sediments. [Reference #1]

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

13.1.4 Skin, Eye, and Respiratory Irritations

Not irritating in Primary Eye Irritation Test. Not irritating to skin in a Primary Dermal Irritation Test. /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.3 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

13.2 Fire Fighting

13.2.1 Fire Fighting Procedures

Suitable extinguishing media: Use **water** spray, alcohol-resistant foam, dry chemical or **carbon dioxide**.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Advice for firefighters: Wear self contained breathing apparatus for fire fighting if necessary.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.3 Accidental Release Measures

13.3.1 Cleanup Methods

ACCIDENTAL RELEASE MEASURES: Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Avoid breathing dust. Environmental precautions: Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided. Methods and materials for containment and cleaning up: Pick up and arrange disposal without creating dust. Sweep up and shovel. Keep in suitable, closed containers for disposal.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.3.2 Disposal Methods

SRP: Recycle any unused portion of the material for its approved use or return it to the manufacturer or supplier. Ultimate disposal of the chemical must consider: the material's impact on air quality; potential migration in air, soil or **water**; effects on animal, aquatic and plant life; and conformance with environmental and public health regulations. If it is possible or reasonable use an alternative chemical product with less inherent propensity for occupational harm/injury/toxicity or environmental contamination.

▸ **Hazardous Substances Data Bank (HSDB)**

Product: Offer surplus and non-recyclable solutions to a licensed disposal company. Contaminated packaging: Dispose of as unused product.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.3.3 Preventive Measures

Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Avoid breathing dust. Environmental precautions: Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Precautions for safe handling: Avoid contact with skin and eyes. Avoid formation of dust and aerosols. Provide appropriate exhaust ventilation at places where dust is formed.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Appropriate engineering controls: Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

SRP: Local exhaust ventilation should be applied wherever there is an incidence of point source emissions or dispersion of regulated contaminants in the work area. Ventilation control of the contaminant as close to its point of generation is both the most economical and safest method to minimize personnel exposure to airborne contaminants. Ensure that the local ventilation moves the contaminant away from the worker.

▸ **Hazardous Substances Data Bank (HSDB)**

13.4 Handling and Storage

13.4.1 Storage Conditions

Keep container tightly closed in a dry and well-ventilated place. Keep in a dry place.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Safe Storage of Pesticides. Always store pesticides in their original containers, complete with labels that list ingredients, directions for use, and first aid steps in case of accidental poisoning. Never store pesticides in cabinets with or near food, animal feed, or medical supplies. Do not store pesticides in places where flooding is possible or in places where they might spill or leak into wells, drains, ground **water**, or surface **water**.

USEPA/Prevention, Pesticides, and Toxic Substances; Citizen's Guide to Pest Control and Pesticide Safety p.23 (September 1995) EPA 730-K-95-001

▸ **Hazardous Substances Data Bank (HSDB)**

13.5 Exposure Control and Personal Protection

13.5.1 Allowable Tolerances

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following raw agricultural commodities:

Commodity	Parts per million
Alfalfa, forage	30.0
Alfalfa, hay	65.0
Almond hulls	17
Apple, wet, pomace	10
Artichoke, globe	6.0
Avocado	1.5
Banana, import (No USA registration as of September 16, 2009)	0.40
Berry, low growing, subgroup 13-07G, except cranberry	4.5
Brassica, head and stem, subgroup 5A	3.0
Brassica, leafy greens, subgroup 5B	18.0
Bushberry subgroup 13-07B	13.0
Caneberry subgroup 13-07A	10.0
Canistel	1.5
Canola, refined oil	5.0
Citrus, dried pulp	4.5
Citrus, oil	85.0
Coffee, green bean, import (No USA registrations as of September 16, 2009)	0.05
Cotton, gin byproducts	55.0
Cucumber	0.5
Dill, seed	100
Endive, Belgium	6.0
Fruit, citrus, group 10-10	2.0
Fruit, pome, group 11-10	3.0
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	5.0
Fruit, stone, group 12-12	3.5
Grain, aspirated fractions	3.0
Grape, raisin	8.5
Herb subgroup 19A	150

Commodity	Parts per million
Hops, cones, dried	35
Leaf petioles subgroup 4B	45
Leafy greens subgroup 4A, except head lettuce and leaf lettuce	60
Lettuce, head	6.5
Lettuce, leaf	11.0
Mango	1.5
Nut, tree, group 14-12	0.70
Oilseed grup 20	3.5
Papaya	1.5
Pea and bean, dried shelled, except soybean, subgroup 6C, except cowpea, field pea and grain lupin	2.5
Pea and bean, succulent shelled, subgroup 6B, except cowpea	0.6
Peanut	0.05
Peanut, meal	0.15
Peanut, refined oil	0.15
Peppermint, tops	30.0
Persimmon	8.0
Sapodilla	1.5
Sapote, black	1.5
Sapote, mamey	1.5
Soybean, hulls	0.2
Soybean, seed	0.1
Soybean, vegetable	2.0
Spearmint, tops	30.0
Star apple	1.5
Turnip, greens	40.0
Vegegable, bulb, group 3-07	5.0
Vegetable, cucurbit, group 9, except cucumber	1.6
Vegetable, fruiting, group 8-10	3.0
Vegetable, legume, edible podded, subgroup 6A	1.6
Vegetable, root, subgroup 1A, except sugar beet, garden beet, radish, and turnip	1.0
Vegetable, tuberous and corm, subgroup 1C	0.05

40 CFR 180.589(a)(1); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), and metabolites 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide and glucuronic acid conjugate of 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide, calculated as the stoichiometric equivalent of boscalid in or on the following food commodities:

Commodity	Parts per million
Cattle, fat	0.30
Cattle, meat	0.10
Cattle, meat byproducts	0.35
Egg	0.02
Goat, fat	0.30
Goat, meat	0.10
Goat, meat byproducts	0.35
Hog, fat	0.20
Hog, meat	0.05
Hog, meat byproducts	0.10
Horse, fat	0.30
Horse, meat	0.10
Horse, meat byproducts	0.35
Milk	0.10
Poultry, fat	0.20
Poultry, meat	0.05
Poultry, meat byproducts	0.20
Sheep, fat	0.30
Sheep, meat	0.10
Sheep, meat byproducts	0.35

40 CFR 180.589(a)(2); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

Time-limited tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in connection with use of the pesticide under section 18 emergency exemptions granted by EPA. Compliance with the tolerance level specified below is to be determined by measuring only boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl). This tolerance will expire and is revoked on the date specified in the following table:

Commodity	Parts per million	Expiration/Revocation Date
Endive, Belgian	16	12/31/13

40 CFR 180.589(b); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

Tolerances are established for the indirect or inadvertent residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following commodities:

Commodity	Parts per million
Animal feed, nongrass, group 18, forage, except alfalfa	1.0
Animal feed, nongrass, group 18, hay, except alfalfa	2.0
Animal feed, nongrass, group 18, seed	0.05
Beet, garden, roots	0.1
Beet, sugar, roots	0.1
Cowpea, seed	0.1
Grain, cereal, forage, fodder and straw, group 16, forage	2.0
Grain, cereal, forage, fodder and straw, group 16, stover	1.5
Grain, cereal, forage, fodder and straw, group 16, straw	3.0
Grain, cereal, group 15	0.20
Grass, forage, fodder, and hay, group 17, forage	2.0
Grass, forage, fodder, and hay, group 17, hay	8.0
Grass, forage, fodder, and hay, group 17, seed screenings	0.20
Grass, forage, fodder, and hay, group 17, straw	0.30
Lupin, grain, grain	0.1
Pea,, field, seed	0.1
Radish, roots	0.1
Rice, hulls	0.50
Turnip, roots	0.1
Vegetable, foliage of legume, group 7, forage	1.5
Vegetable, foliage of legume, group 7, hay	2.0
Vegetable, foliage of legume, group 7, vines	0.05
Vegetable, leafy, except brassica, group 4, except celery, lettuce and spinach	1.0
Vegetable, leaves of root and tuber, group 2	0.1

*40 CFR 180.589(d); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: **https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

13.5.2 Personal Protective Equipment (PPE)

Eye/face protection: Safety glasses with side-shields conforming to EN166. Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

Skin protection: Handle with gloves.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

Body Protection: Impervious clothing. The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

Respiratory protection: For nuisance exposures use type P95 (US) or type P1 (EU EN 143) particle respirator. For higher level protection use type OV/AG/P99 (US) or type ABEK-P2 (EU EN 143) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

13.6 Regulatory Information

13.6.1 State Drinking Water Guidelines

(ME) MAINE 152.6 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

Hazardous Substances Data Bank (HSDB)

13.6.2 FIFRA Requirements

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following raw agricultural commodities:

Commodity
Alfalfa, forage
Alfalfa, hay
Almond hulls
Apple, wet, pomace
Artichoke, globe
Avocado
Banana, import (No USA registration as of September 16, 2009)
Berry, low growing, subgroup 13-07G, except cranberry
Brassica, head and stem, subgroup 5A

Commodity
Brassica, leafy greens, subgroup 5B
Bushberry subgroup 13-07B
Caneberry subgroup 13-07A
Canistel
Canola, refined oil
Citrus, dried pulp
Citrus, oil
Coffee, green bean, import (No USA registrations as of September 16, 2009)
Cotton, gin byproducts
Cucumber
Dill, seed
Endive, Belgium
Fruit, citrus, group 10-10
Fruit, pome, group 11-10
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F
Fruit, stone, group 12-12
Grain, aspirated fractions
Grape, raisin
Herb subgroup 19A
Hops, cones, dried
Leaf petioles subgroup 4B
Leafy greens subgroup 4A, except head lettuce and leaf lettuce
Lettuce, head
Lettuce, leaf
Mango
Nut, tree, group 14-12
Oilseed grup 20
Papaya
Pea and bean, dried shelled, except soybean, subgroup 6C, except cowpea, field pea and grain lupin
Pea and bean, succulent shelled, subgroup 6B, except cowpea
Peanut
Peanut, meal
Peanut, refined oil
Peppermint, tops

Commodity
Persimmon
Sapodilla
Sapote, black
Sapote, mamey
Soybean, hulls
Soybean, seed
Soybean, vegetable
Spearmint, tops
Star apple
Turnip, greens
Vegegable, bulb, group 3-07
Vegetable, cucurbit, group 9, except cucumber
Vegetable, fruiting, group 8-10
Vegetable, legume, edible podded, subgroup 6A
Vegetable, root, subgroup 1A, except sugar beet, garden beet, radish, and turnip
Vegetable, tuberous and corm, subgroup 1C

40 CFR 180.589(a)(1); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), and metabolites 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide and **glucuronic acid** conjugate of 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide, calculated as the stoichiometric equivalent of boscalid in or on the following food commodities:

Commodity
Cattle, fat
Cattle, meat
Cattle, meat byproducts
Egg
Goat, fat
Goat, meat
Goat, meat byproducts
Hog, fat
Hog, meat
Hog, meat byproducts

Commodity
Horse, fat
Horse, meat
Horse, meat byproducts
Milk
Poultry, fat
Poultry, meat
Poultry, meat byproducts
Sheep, fat
Sheep, meat
Sheep, meat byproducts

40 CFR 180.589(a)(2); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Time-limited tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in connection with use of the pesticide under section 18 emergency exemptions granted by EPA. Compliance with the tolerance level specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl). This tolerance will expire and is revoked on the date specified in the following table:

Commodity	Expiration/Revocation Date
Endive, Belgian	12/31/13

40 CFR 180.589(b); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Tolerances are established for the indirect or inadvertent residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following commodities:

Commodity
Animal feed, nongrass, group 18, forage, except alfalfa
Animal feed, nongrass, group 18, hay, except alfalfa
Animal feed, nongrass, group 18, seed
Beet, garden, roots
Beet, sugar, roots
Cowpea, seed
Grain, cereal, forage, fodder and straw, group 16, forage
Grain, cereal, forage, fodder and straw, group 16, stover
Grain, cereal, forage, fodder and straw, group 16, straw
Grain, cereal, group 15

Commodity
Grass, forage, fodder, and hay, group 17, forage
Grass, forage, fodder, and hay, group 17, hay
Grass, forage, fodder, and hay, group 17, seed screenings
Grass, forage, fodder, and hay, group 17, straw
Lupin, grain, grain
Pea,, field, seed
Radish, roots
Rice, hulls
Turnip, roots
Vegetable, foliage of legume, group 7, forage
Vegetable, foliage of legume, group 7, hay
Vegetable, foliage of legume, group 7, vines
Vegetable, leafy, except brassica, group 4, except celery, lettuce and spinach
Vegetable, leaves of root and tuber, group 2

40 CFR 180.589(d); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Pesticide Fact Sheet for Boscalid: Reason for Issuance: New Chemical; Date Issued: July 2003.

USEPA; Office of Prevention, Pesticides and Toxic Substances, Pesticide Fact Sheet for Boscalid p.1 (July 2003). Available from, as of October 4, 2016: ***https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-128008_01-Jul-03.pdf***

▸ **Hazardous Substances Data Bank (HSDB)**

13.7 Other Safety Information

13.7.1 Toxic Combustion Products

Special hazards arising from the substance or mixture: Carbon oxides, nitrogen oxides (NOx), **Hydrogen chloride** gas.

Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: ***https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.7.2 Special Reports

USEPA; Office of Prevention, Pesticides and Toxic Substances, Pesticide Fact Sheet for Boscalid, Reason for Issuance: New Chemical (July 2003).[Available from, as of June 24, 2016: https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-128008_01-Jul-03.pdf]

- Hazardous Substances Data Bank (HSDB)

14 Toxicity

14.1 Toxicological Information

14.1.1 Toxicity Summary

IDENTIFICATION AND USE: Boscalid is a solid. It is used as fungicide, plant health product, seed treatment/protectant. HUMAN EXPOSURE AND TOXICITY: Boscalid may be genotoxic and cytotoxic in vitro in human peripheral blood lymphocytes. ANIMAL STUDIES: Boscalid has a low toxicity in animal studies. In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased body weights and body weight gains and effects on the liver (increase in weights, changes in enzyme levels and histopathological changes) as well as on the thyroid (increase in weights and histopathological changes). In a developmental toxicity study in rats, no developmental toxicity was observed in the fetuses at the highest dose tested. In a developmental toxicity study in rabbits, an increased incidence of abortions or early delivery was observed at the limit dose. The does and fetuses were equally sensitive to the test material. In a 2-generation reproduction study in rats, the NOAEL for parental toxicity was based on decreased body weight and body weight gain as well as hepatocyte degeneration. No reproductive toxicity was observed in this study at the highest dose tested. There was quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats, where decreases in pup body weights and body weight gains were seen in the absence of any maternal toxicity. In a two-year chronic toxicity study and a two-year carcinogenicity study in male and female rats, the combined data showed that, for thyroid follicular cell adenomas, males had a significant increasing trend, when compared with controls. There was no treatment-related increase in thyroid follicular cell carcinomas. The increase in thyroid follicular cell adenomas appeared to be treatment-related in males. Regarding females, combined data from the two rat studies indicated that there was an increasing trend for thyroid follicular cell adenomas. No carcinomas were observed in female. Boscalid was tested in five mutagenicity studies and was found to be negative in all of them. ECOTOXICITY STUDIES: Boscalid is categorized as practically nontoxic to birds in both an acute and subacute studies. Boscalid was harmless to adult Galendromus occidentalis. Boscalid use does not represent a risk to plants. Commercial producers of honey bee queens (Apis mellifera L.) have reported unexplained loss of immature queens during the larval or pupal stage. Many affected queen-rearing operations are situated among the almond orchards of California and report these losses in weeks after almond trees bloom. Almond flowers are a rich foraging resource for bees, but are often treated with fungicides, insecticides, and spray adjuvants during bloom. Anecdotal reports by queen producers associate problems in queen development with application of the fungicide Pristine (boscalid and **pyraclostrobin**). Chemical analysis revealed that low concentrations of **pyraclostrobin** (50 ppb), but no boscalid, were detectable in royal jelly secreted by nurse bees feeding on treated pollen.

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.2 Evidence for Carcinogenicity

Cancer Classification: Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential

USEPA Office of Pesticide Programs, Health Effects Division, Science Information Management Branch: "Chemicals Evaluated for Carcinogenic Potential" (April 2006)

▸ **Hazardous Substances Data Bank (HSDB)**

The EPA classified Boscalid (BAS 510 F) as, "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", and, therefore, the quantification of human cancer risk is not recommended. The cancer classification was based on the following weight of evidence considerations. First, in male Wistar rats, there was a significant trend (but not pair wise comparison) for the combined thyroid adenomas and carcinomas. This trend was driven by the increase in adenomas. Second, in the female rats, there was only a borderline significant trend for thyroid adenomas (there were no carcinomas)...

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.12 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.3 Carcinogen Classification

Carcinogen Classification	Not listed by IARC.

- Toxin and Toxin Target Database (T3DB)

14.1.4 Adverse Effects

Occupational hepatotoxin - Secondary hepatotoxins: the potential for toxic effect in the occupational setting is based on cases of poisoning by human ingestion or animal experimentation.

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

14.1.5 Toxicity Data

LC50 (rat) > 6,700 mg/m3

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

14.1.6 Antidote and Emergency Treatment

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing **water**. Do not induce vomiting. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

- Hazardous Substances Data Bank (HSDB)

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer **oxygen** by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with **water**. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of **water** for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

- Hazardous Substances Data Bank (HSDB)

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag-valve-mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta agonist such as **albuterol** for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W TKO. Use 0.9% saline (NS) or lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with **diazepam** (**Valium**) or **lorazepam** (**Ativan**) ... . Use **proparacaine hydrochloride** to assist eye irrigation ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160-61

- Hazardous Substances Data Bank (HSDB)

14.1.7 Human Toxicity Excerpts

/GENOTOXICITY/ The aim of this study was to investigate the genotoxic and cytotoxic potential of the Signum fungicide and its active ingredients (boscalid and **pyraclostrobin**) on human peripheral blood lymphocytes using the cytokinesis-block micronucleus (CBMN) assay. Micronuclei (MNi), nucleoplasmic bridges (NPBs), nuclear bud (NBUDs) formations, and the cytokinesis-block proliferation index (CBPI) were evaluated in treated lymphocytes in Go (cells were treated and then kept in culture without stimulation for 24 hr) and proliferation phases (cells were treated after 44 hr culture in medium containing phytohemagglutinin). MN formation in lymphocytes treated in G0 statistically increased at doses of 2, 6, and 25 ug/mL signum; 0.5 and 2 ug/mL boscalid; and 0.5, 1.5, and 2 ug/mL **pyraclostrobin**; while NPB formation increased at a dose of 0.25 ug/mL **pyraclostrobin**. All concentrations of each fungicide did not statistically increase NBUD formation, while the cytotoxicity increased the dependent on concentration in lymphocytes treated in G0 . Doses of 0.5, 1, 1.5, and 3 ug/mL signum; 0.5, 1, and 1.5 ug/mL boscalid; and 0.75 ug/mL **pyraclostrobin** statistically increased the MN formation in proliferating lymphocytes. NPB formation increased in proliferating lymphocytes at doses of 1, 1.5, 2, and 3 ug/mL signum and at a dose of 0.75 ug/mL **pyraclostrobin**. In addition, a dose of 0.75 ug/mL **pyraclostrobin** increased NBUD frequencies. Cytotoxicity increased with increasing concentrations of each fungicide. It is concluded that signum, boscalid, and **pyraclostrobin** may be genotoxic and cytotoxic in vitro human peripheral blood lymphocytes in consideration of each of the two protocols.

PMID:22730168

Cayir A et al; Environ Toxicol 29 (7): 723-32 (2014)

▸ **Hazardous Substances Data Bank (HSDB)**

/ALTERNATIVE and IN VITRO TESTS/ Nonpersistent pesticides are considered less harmful for the environment, but their impact as endocrine disruptors has not been fully explored. The pesticide Switch was applied to grape vines, and the maximum residue concentration of its active ingredients was quantified. The transactivation potential of the pesticides Acorit, Frupica, Steward, **Reldan**, Switch, Cantus, **Teldor**, and Scala and their active compounds (**hexythiazox**, **mepanipyrim**, **indoxacarb**, **chlorpyrifos-methyl**, **cyprodinil**, **fludioxonil**, boscalid, **fenhexamid**, and **pyrimethanil**) were tested on human estrogen receptor alpha (ERalpha), androgen receptor (AR) and arylhydrocarbon receptor (AhR) in vitro. Relative binding affinities of the pure pesticide constituents for AR and their effect on human breast cancer and prostate cancer cell lines were evaluated. Residue concentrations of Switch's ingredients were below maximum residue limits. **Fludioxonil** and **fenhexamid** were ERalpha agonists (EC50 -values of 3.7 and 9.0 uM, respectively) and had time-dependent effects on endogenous ERalpha-target gene expression (cyclin D1, **progesterone** receptor, and nuclear respiratory factor 1) in MCF-7 human breast cancer cells. **Fludioxonil**, **mepanipyrim**, **cyprodinil**, **pyrimethanil**, and **chlorpyrifos-methyl** were AhR-agonists (EC50 s of 0.42, 0.77, 1.4, 4.6, and 5.1 uM, respectively). Weak AR binding was shown for **chlorpyrifos-methyl**, **cyprodinil**, **fenhexamid**, and **fludioxonil**. Assuming a total uptake which does not take metabolism and clearance rates into account, our in vitro evidence suggests that pesticides could activate pathways affecting hormonal balance, even within permitted limits, thus potentially acting as endocrine disruptors.

PMID:23436777

Medjakovic S et al; Environ Toxicol 29 (10): 1201-16 (2014)

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.8 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 90-Day oral toxicity rodents (rats). NOAEL: 34/159 mg/kg/day (M/F); LOAEL: 137/395 mg/kg/day (M/F): M = increases in absolute and relative thyroid weights and increased incidence of thyroid hyperplasia as well as follicular epithelial hypertrophy; F = increases in absolute and relative thyroid weights. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 90-Day oral toxicity rodents (mice). NOAEL: 197/2209 mg/kg/day (M/F); LOAEL: 788/2209 mg/kg/day (M/F): M = increased liver weights and increased incidence of marked fatty change in the liver; F = not attained. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 90-Day oral toxicity in nonrodents (dogs). NOAEL: 7.6/8.1 mg/kg/day (M/F); LOAEL: 78.1/81.7 mg/kg/day (M/F): M = increased alkaline phosphatase activity and hepatic weights; F = increased alkaline phosphatase activity and hepatic weights. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 21/28-Day dermal toxicity (rats). NOAEL: 1000 mg/kg/day (Highest Dose Tested); LOAEL: >1000 mg/kg/day /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

For more Non-Human Toxicity Excerpts (Complete) data for BOSCALID (36 total), please visit the **HSDB record page**.

Hazardous Substances Data Bank (HSDB)

14.1.9 Non-Human Toxicity Values

LD50 Rat oral >5,000 mg/kg (Technical boscalid) /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.3 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

LD50 Rat dermal >2,000 mg/kg (Technical boscalid) /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.3 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

14.1.10 Ecotoxicity Values

EC50; Species: Danio rerio (Zebra Danio) age 6-8 hr postfertilization embryo; Conditions: freshwater, renewal, 26 °C; Concentration: 1.1337 uM for 120 hr; Effect: multiple effects: increased mortality, deformation; decreased hatch /formulation/

Padilla S et al; Reprod Toxicol 33 (2): 174-187 (2012) as cited in the ECOTOX database. Available from, as of July 13, 2016

Hazardous Substances Data Bank (HSDB)

14.1.11 Ecotoxicity Excerpts

/BIRDS and MAMMALS/ Risk to Avian Species (Acute/Chronic). Boscalid is categorized as practically nontoxic to birds in both an acute and subacute exposure basis, no acute levels of concern (LOC) are exceeded for birds feeding on any of the modeled food items (short grass, tall grass, broadleaf plants insects and seeds). However, chronic exposure to boscalid at the proposed application rate for strawberries, i.e., 5 applications of 0.350 lbs a.i./A with a 7-day reapplication interval, results in the chronic risk level of concern being exceeded for birds feeding on short grasses (RQ=1.08). Exposure to boscalid on other avian food items (tall grasses, broadleaf plants/insects, and seeds) at this application rate did not result in any exceedance of either acute or chronic LOCs. Based on maximum estimated concentrations on short grass the chronic risk LOC would be exceeded for approximately 4 days; however, if mean foliar residues were used to estimate exposure, chronic avian LOCs would not have been exceeded since mean foliar residues are roughly half maximum exposure values.

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.16 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

/AQUATIC SPECIES/ The presence of fungicides in the marine environment may pose risks to marine organisms, but little is known about fungicide effects on these organisms, especially invertebrates. The present study investigated the effects of the commonly used boscalid fungicide Filan on life history traits, feeding rate, and energy reserves (lipid, **glycogen**, and protein content)

of the marine amphipod Allorchestes compressa over 6 wk under laboratory conditions. Amphipods were exposed to 3 concentrations of Filan (1 ug, 10 ug, and 40 ug active ingredient [a.i.]/L), with 5 replicates per treatment. Lipid content and reproduction were the most sensitive measures of effect, with lipid content reduced by 53.8% at the highest concentration. Survival, growth, and other energy reserves of amphipods were also negatively affected by Filan, and the effects were concentration dependent. Antennal deformities were incidentally observed on the amphipods at a concentration of 40 ug a.i./L. The results of the present study indicate comprehensive effects of the boscalid fungicide Filan on A. compressa at environmentally relevant concentrations. The decline or absence of A. compressa in marine ecosystems could impair the ecosystem function because of their important role in trophic transfer and nutrient recycling. The authors' results suggest that even though the use of fungicides is often regarded as posing only a minor risk to aquatic organisms, the assessment of their long-term effects is critical.

PMID:26378894

Vu HT et al; Environ Toxicol Chem 35 (5): 1130-7 (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

/AQUATIC SPECIES/ Boscalid is moderately toxic to aquatic animals; however based on estimated exposure concentrations, the proposed uses of boscalid are not likely to represent a threat to either acute or chronic ecological risk to freshwater fish and invertebrates or to estuarine/marine fish at a maximum proposed multiple application rates as high as six applications of 0.350 lbs. a.i./A. However, the acute risk level of concern for endangered species is exceeded for estuarine/marine invertebrates. While boscalid is not expected to adversely affect aquatic animals whose lives are primarily spent in open **water**, bottom-dwelling (benthic) fauna may be more likely to encounter boscalid based on the chemical's persistence and tendency to sorb to sediments. Modeling of benthic exposure, based on a closed farm pond scenario over a 36-year period, did not exceed the chronic risk level of concern for sediment-dwelling animals.

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.16 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

/OTHER TERRESTRIAL SPECIES/ A laboratory evaluation of **fenbuconazole**, **myclobutanil propiconazole**, boscalid, **fenhexamid** and **pyraclostrobin** revealed these fungicides to be harmless to adult Galendromus occidentalis /mite/. None of these fungicides affected adversely fecundity and egg viability. Elemental **sulphur** also had no effect on adults and fecundity. However, 72.4% of the young larvae perished after hatching. The six novel fungicides are safer alternatives to **sulphur** in perennial crops in British Columbia.

PMID:18792796

Bostanian NJ et al; Exp Appl Acarol 47 (1): 63-9 (2009)

▸ **Hazardous Substances Data Bank (HSDB)**

For more Ecotoxicity Excerpts (Complete) data for BOSCALID (10 total), please visit the **HSDB record page**.

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.12 Ongoing Test Status

EPA has released the Interactive Chemical Safety for Sustainability (iCSS) Dashboard. The iCSS Dashboard provides an interactive tool to explore rapid, automated (or in vitro high-throughput) chemical screening data generated by the Toxicity Forecaster (ToxCast) project and the federal Toxicity Testing in the 21st century (Tox21) collaboration. /The title compound was tested by ToxCast and/or Tox21 assays/[USEPA; ICSS Dashboard Application; Available from, as of July 7, 2016: http://actor.epa.gov/dashboard/]

▸ **Hazardous Substances Data Bank (HSDB)**

14.2 Ecological Information

14.2.1 EPA Ecotoxicity

Pesticide Ecotoxicity Data from EPA

EPA Pesticide Ecotoxicity Database

14.2.2 Environmental Fate/Exposure Summary

Boscalid's production may result in its release to the environment through various waste streams; its use as a fungicide will result in its direct release to the environment. If released to air, a vapor pressure of 5.4X10-10 mm Hg at 20 °C indicates boscalid will exist solely in the particulate phase in the atmosphere. Particulate-phase boscalid will be removed from the atmosphere by wet and dry deposition. Boscalid is stable to photolysis in **water** and, therefore, is not expected to be susceptible to direct photolysis by sunlight. If released to soil, boscalid is expected to be immobile based upon an estimated Koc of 9500. Volatilization from moist soil surfaces is not expected to be an important fate process based upon a Henry's Law constant of 5.11X10-11 atm-cu m/mole. Boscalid is not expected to volatilize from dry soil surfaces based upon its vapor pressure. Biodegradation half-lives in soil ranging from 96 to 578 days indicate that biodegradation is not an important environmental fate process in soil or **water**. If released into **water**, boscalid is expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from **water** surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 42 suggests the potential for bioconcentration in aquatic organisms is moderate. Boscalid is stable to hydrolysis. Occupational exposure to boscalid may occur through inhalation and dermal contact with this compound at workplaces where boscalid is produced or used. Monitoring data indicate that the general population may be exposed to boscalid via ingestion of some fruits and wines, dermal contact with spray in the vicinity of farms applying boscalid and contact with contaminated surface **water** or sediments in agricultural regions using this fungicide. (SRC)

Hazardous Substances Data Bank (HSDB)

14.2.3 Artificial Pollution Sources

Boscalid's production may result in its release to the environment through various waste streams; its use as a fungicide(1) will result in its direct release to the environment(SRC).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

14.2.4 Environmental Fate

TERRESTRIAL FATE: Based on a classification scheme(1), an estimated Koc value of 9500(SRC), determined from a structure estimation method(2), indicates that boscalid is expected to be immobile in soil(SRC). Volatilization of boscalid from moist soil surfaces is not expected to be an important fate process(SRC) given a Henry's Law constant of 5.11X10-11 atm-cu m/mole(3). Boscalid is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 5.4X10-10 mm Hg at 20 °C(3). Biodegradation half-lives in soil ranging from 96 to 578 days(4) indicate that biodegradation is not an important environmental fate process in soil(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

TERRESTRIAL FATE: Boscalid is generally persistent in the field based on terrestrial dissipation studies employing both cropped and bare plots in the US and Canada(1). The DT50 dissipation rate ranged from 27 to 372 days, generally being greater than 100 days(1).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

TERRESTRIAL FATE: The aim of this study was to analyze the environmental fate of the fungicide boscalid in a sandy soil. Boscalid was applied in spring 2010/11 to a cropland site in western Germany. Three years after second application 65 undisturbed soil samples were taken. Boscalid was extracted using accelerated solvent extraction (ASE). Boscalid contents in the plough horizon ranged between 0.12 and 0.53 with a field mean of 0.20 +/- 0.09 ug/kg. These contents were considerably lower compared to calculation using literature DT50 values, whereby a concentration of 16.89 ug kg/L was expected assuming a literature DT50 value of 345 days. Therefore, the measured field boscalid concentration only yields 1.2% of the expected value. To test whether the unknown extraction efficiency, losses from spray drift and interception can explain the mismatch between calculated and measured concentrations all these uncertainties were taken into account into calculations, but field concentrations and DT50 were still lower as expected. Leaching to deeper horizons was also studied but could not explain the discrepancy either. Moreover, a short-term incubation experiment using (14)C-labelled boscalid revealed also shorter DT50 values of 297-337 compared to the 345 days taken from literature. However, this DT50 value is still considerably larger compared to the 104-224 days that were calculated based on the field experiment. Our results indicate that boscalid dissipation under field conditions is much faster at agricultural sites with sandy soil type than expected from laboratory incubation experiments.

PMID:26688253

Karlsson AS et al; Chemosphere 14: 163-73 (2016)

Hazardous Substances Data Bank (HSDB)

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 9500(SRC), determined from a structure estimation method(2), indicates that boscalid is expected to adsorb to suspended solids and sediment(SRC). Volatilization from **water** surfaces is not expected(3) based upon a Henry's Law constant of 5.11X10-11 atm-cu m/mole(4). According to a classification scheme(5), an estimated BCF of 42(SRC), from its log Kow of 2.96(4) and a regression-derived equation(2), suggests the potential for bioconcentration in aquatic organisms is moderate(SRC). Biodegradation half-lives in soil ranging from 96 to 578 days(6) indicate that biodegradation is not an important environmental fate process in **water**(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

For more Environmental Fate (Complete) data for BOSCALID (6 total), please visit the **HSDB record page**.

Hazardous Substances Data Bank (HSDB)

14.2.5 Environmental Biodegradation

AEROBIC: A biodegradation half-life in soil ranging from 96 to 578 days and a dissipation half-life range of 27 to 372 days(1) indicate that boscalid is not expected to biodegrade rapidly under aerobic conditions(SRC).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

ANAEROBIC: Boscalid is stable in soil under anaerobic conditions(1).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

14.2.6 Environmental Abiotic Degradation

Boscalid is stable to hydrolysis at pH 5, 7 and 9 as indicated by no change to ring-labeled bocalid at a concentration of 3 mg active ingredient/L maintained in sterile aqueous buffer solutions for 30 days(1). Boscalid is stable to photolysis in **water**(2); 3 ug/L active ingredient remained unchanged following exposure to continuous irradiation using a **xenon** lamp for 15 days(1).

*(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub. Available from, as of May 11, 2016: **https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1:** (2) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)*

Hazardous Substances Data Bank (HSDB)

14.2.7 Environmental Bioconcentration

An estimated BCF of 42 was calculated in fish for boscalid(SRC), using a log Kow of 2.96(1) and a regression-derived equation(1). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is moderate(SRC). Accumulation is expected to be greatest in non-edible versus edible tissue and should depurate rapidly once organism is no longer exposed(4).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

14.2.8 Soil Adsorption/Mobility

The Koc of boscalid is estimated as 9500(SRC), using a log Kow of 2.96(1) and a regression-derived equation(2). According to a classification scheme(3), this estimated Koc value suggests that boscalid is expected to be immobile in soil(SRC). Boscalid is expected to sorb to aquatic sediments(4).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

Buffer zones such as ponds and ditches are used to reduce field-scale losses of pesticides from subsurface drainage waters to surface waters. The objective of this study was to assess the efficiency of these buffer zones, in particular constructed wetlands, focusing specifically on sorption processes. We modelled the sorption processes of three herbicides [**2-methyl-4-chlorophenoxyacetic acid** (**2,4-MCPA**), **isoproturon** and **napropamide**] and three fungicides (boscalid, **prochloraz** and **tebuconazole**) on four substrates (two soils, sediment and straw) commonly found in a pond and ditch in Lorraine (France). A wide range of Freundlich coefficient (K fads) values was obtained, from 0.74 to 442.63 mg(1 - n) L (n) kg(-1), and the corresponding K foc values ranged from 56 to 3,725 mg(1 - n) L (n) kg(-1). Based on potential retention, the substrates may be classified as straw >> sediments > soils. These results show the importance of organic **carbon** content and nature in the process of sorption. Similarly, the studied pesticides could be classified according to their adsorption capacity as follows: **prochloraz** >> **tebuconazole**-boscalid > **napropamide** >> **MCPA-isoproturon**. This classification is strongly influenced by the physico-chemical properties of pesticides, especially solubility and K oc. Straw exhibited the largest quantity of non-desorbable pesticide residues, from 12.1 to 224.2 mg/L for all pesticides. The presence of plants could increase soil-sediment sorption capacity. Thus, establishment and maintenance of plants and straw filters should be promoted to optimize sorption processes and the efficiency of ponds and ditches in reducing surface **water** pollution.

PMID:23784054
Vallee R et al; Environ Sci Pollut Res Int 21(7): 4895-905 (2014)

Hazardous Substances Data Bank (HSDB)

14.2.9 Volatilization from Water/Soil

The Henry's Law constant for boscalid is 5.11X10-11 atm-cu m/mole(1). This Henry's Law constant indicates that boscalid is expected to be essentially nonvolatile from water surfaces(2). Boscalid is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 5.4X10-10 mm Hg(1).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990)

Hazardous Substances Data Bank (HSDB)

14.2.10 Environmental Water Concentrations

GROUNDWATER: Boscalid was not reported in groundwater samples taken from Italy in the regions of the Po River, Arno River, unspecified rivers in Tuscany, or the Fuscino Plain); research was conducted from 1997 through 2013(1).

PMID:24602913

(1) Meffe R, de Bustamante I; Sci Total Environ 481: 280-295 (2014)

Hazardous Substances Data Bank (HSDB)

SURFACE WATER: The US Geological Survey conducted a study of 33 fungicides and an additional 57 current-use pesticides applied to streams, ponds, and shallow groundwater located in areas of intense fungicide use within three geographic areas across the United States. Sampling sites were selected near or within farms using prophylactic fungicides at rates and types typical of their geographic location. Boscalid was detected in 72% of samples(1,2).

*(1) Reilly TJ et al; Chemosphere 89: 228-34 (2012). Available from, as of May 11, 2016: **https://www.ncbi.nlm.nih.gov/pubmed/?term=22564453** (2) USGS; Fungicides from Areas of Intense use Detected in Streams and Groundwater. Washington, DC: US Geol Survey. Environmental Health - Toxic Substances. Science Features. Available from, as of May 13, 2016: **https://toxics.usgs.gov/highlights/fungicide_occurrence.html***

Hazardous Substances Data Bank (HSDB)

SURFACE WATER: Boscalid was reported at a maximum concentration of 2,000 ng/L in an unspecified surface water sample taken from Italy (Po River, Arno River, unspecified rivers in Tuscany, or surface waters of the Fuscino Plain); research was conducted from 1997 through 2013(1).

PMID:24602913

(1) Meffe R, de Bustamante I; Sci Total Environ 481: 280-295 (2014)

Hazardous Substances Data Bank (HSDB)

14.2.11 Sediment/Soil Concentrations

SEDIMENT: The US Geological Survey conducted a study of 34 fungicides and an additional 57 current-use pesticides in bed sediments and suspended solids collected from areas of intense fungicide use within three geographic areas across the United States. Sampling sites were selected near or within agricultural research farms using prophylactic fungicides at rates and types typical of their geographic location. Boscalid was detected in 53% of sediments collected within highly agricultural areas(1,2).

*(1) Smalling KL et al; Sci Total Environ 447: 179-85 (2013). Available from, as of May 11, 2016: **https://www.ncbi.nlm.nih.gov/pubmed/23380566** (2) USGS; USGS; Fungicides from Areas of Intense use Detected in Streams and Groundwater. Washington, DC: US Geol Survey. Environmental Health - Toxic Substances. Science Features. Available from, as of May 13, 2016: **https://toxics.usgs.gov/highlights/fungicide_occurrence.html***

Hazardous Substances Data Bank (HSDB)

14.2.12 Food Survey Values

The effects of four fungicides commonly used for the control of fungal diseases in vines and grapes in the course of winemaking were tested. The concentration of fungicide residues was monitored throughout the process to establish their kinetics of dissipation. In all cases the percentages of dissipation were >68%, which shows the detoxificant effect of the winemaking process. On the other hand, the effect of the fungicide residues on the aroma composition of Tempranillo red wines was tested. To evaluate possible modifications on the aroma profile of wines, seven odorant series (ripe fruits, fresh fruits, lactic, floral, spicy, vinous, and herbaceous) were built from the odor activity values (OAVs) obtained for each volatile compound. Ripe fruits and fresh fruits were the major aromatic attributes in all Tempranillo red wines. These two odorant series registered the highest variations in their total OAVs with respect to the control wine, especially with the application of boscalid + **kresoxim-methyl** into vines, leading to a decrease in the ripe fruit and fresh fruit nuances of the resulting wines. Moreover, when the effect of these fungicides on the aroma of Tempranillo red wines was compared throughout two years (2012 and 2013), wines elaborated from grapes treated in the field with boscalid + **kresoxim-methyl** in 2013 displayed the highest variation in aroma profile with respect to control wine. During alcoholic fermentation, dissipation half-lives of 4.7 and 5.7 days in 2012 and 2013, respectively, were exhibited for boscalid + **kresoxim-methyl**(1).

PMID:26808836

(1) Boquerol-Paro R et al; J Agric Food Chem 64(6): 1344-54 (2016)

▸ Hazardous Substances Data Bank (HSDB)

Azoxystrobin, boscalid, **cyprodinil**, **fenhexamid**, and **pyrimethanil** are new generation fungicides extensively employed in order to combat diseases affecting vineyards worldwide. Owing to their physico-chemical characteristics, residues of these compounds on grapes are transferred to must and wine. In this study, a survey of the occurrence of these fungicides in international wines was carried out by using rapid antibody-based assays. Results are discussed as a function of wine type and sample geographical origin. 44.4% of the samples contained at least one of the targets (>10 ug/L). Fungicide residue occurrences were 22.4%, 19.2%, 18.8%, 6.8%, and 1.2% for **pyrimethanil**, boscalid, **fenhexamid**, **cyprodinil**, and **azoxystrobin**, respectively, while residue contents higher than 100 ug/L were found in 8.4% of the samples. This study shows that contamination of commercial wines with pesticides is an issue of worldwide relevance with potential implications for consumer health and international trade.

PMID:26593617

Esteve-Turrillas FA et al; Food Chem 196: 1279-86 (2016)

▸ Hazardous Substances Data Bank (HSDB)

Crops grown under plastic-clad structures or in greenhouses may be prone to an increased frequency of pesticide residue detections and higher concentrations of pesticides relative to equivalent crops grown in the open field. To test this we examined pesticide data for crops selected from the quarterly reports (2004-2009) of the UK's Pesticide Residue Committee. Five comparison crop pairs were identified whereby one crop of each pair was assumed to have been grown primarily under some form of physical protection ('protected') and the other grown primarily in open field conditions ('open'). For each pair, the number of detectable pesticide residues and the proportion of crop samples containing pesticides were statistically compared (n=100 samples for each crop). The mean concentrations of selected photolabile pesticides were also compared. For the crop pairings of cabbage ('open') vs. lettuce ('protected') and 'berries' ('open') vs. strawberries ('protected') there was a significantly higher number of pesticides and proportion of samples with multiple residues for the protected crops. Statistically higher concentrations of pesticides, including **cypermethrin**, **cyprodinil**, **fenhexamid**, boscalid and **iprodione** were also found in the protected crops compared to the open crops. The evidence here demonstrates that, in general, the protected crops possess a higher number of detectable pesticides compared to analogous crops grown in the open. This may be due to different pesticide-use regimes, but also due to slower rates of pesticide removal in protected systems. The findings of this study raise implications for pesticide management in protected-crop systems.

PMID:25465948

Allen G et al; Chemosphere 119: 1428-35 (2015)

▸ Hazardous Substances Data Bank (HSDB)

Greenhouse studies were conducted to evaluate the dissipation rate kinetics and estimate the behavior of selected pesticides after washing, peeling, simmering, and canning of tomato expressed as processing factor (PF). Two varieties (Marissa and Harzfeuer) were treated by six fungicides: **azoxystrobin**, boscalid, **chlorothalonil**, **cyprodinil**, **fludioxonil**, and **pyraclostrobin** at single and double dose and risk assessment defined as hazard quotient was performed. The QuEChERS method was used for sample preparation followed by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The dissipation of fungicides approximately fitted to a first-order kinetic model, with half-life values ranging from 2.49 and 2.67 days (**cyprodinil**) to 5.00 and 5.32 days (**chlorothalonil**) for Marissa and Harzfeuer variety, respectively. Results from processing studies showed that treatments have significant effects on the removal of the studied fungicides for both

varieties. The PFs were generally less than 1 (between 0.01 and 0.90) and did not depend on variety. The dietary exposure assessed based on initial deposits of application at single and double dose on tomatoes and concentration after each process with PF correction showed no concern to consumer health. Our results would be a useful tool for monitoring of fungicides in tomatoes and provide more understanding of residue behavior and risk posed by these fungicides.

PMID:26957431
Full text: ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4893063***
Jankowska M et al; Environ Sci Pollut Res Int Mar 9. (e-pub ahead of print) (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

14.2.13 Animal Concentrations

Boscalid is a new-generation fungicide that has been detected in several bee matrices. The objective of this work was to characterize boscalid metabolites in honeybees based on in vivo experimentation, and next to verify the presence of these metabolites into honeybees from colonies presenting troubles. A methodology based on complementary mass spectrometric tools, namely ultra-high performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-QToF) or triple quadrupole mass spectrometry (UHPLC-QqQ) was implemented. Honeybees were sprayed with boscalid, at field rate (to induce the metabolization process) and the parent compound with its generated metabolites were then extracted using modified EU-QuEChERS method. The mass characteristics including exact mass, isotopic profile and mass fragments allowed assuming the structure of several metabolites. Some of them were unambiguously identified by comparison with synthesized analytical standards. The metabolites were resulted from hydroxylation and dechlorination of the parent compound as well as the substitution of a **chlorine** atom with an **hydroxyl** group. The metabolites were then quantified in bee samples collected from various beehives located in France. Boscalid and three of its metabolites were present in some samples at a level ranged between 0.2 and 36.3 ng/g.

PMID:27179242
Jabot C et al; Chemosphere 156: 245-51 (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

There is considerable and ongoing debate as to the harm inflicted on bees by exposure to agricultural pesticides. In part, the lack of consensus reflects a shortage of information on field-realistic levels of exposure. Here, we quantify concentrations of neonicotinoid insecticides and fungicides in the pollen of oilseed rape, and in pollen of wildflowers growing near arable fields. We then compare this to concentrations of these pesticides found in pollen collected by honey bees and in pollen and adult bees sampled from bumble bee colonies placed on arable farms. We also compared this with levels found in bumble bee colonies placed in urban areas. Pollen of oilseed rape was heavily contaminated with a broad range of pesticides, as was the pollen of wildflowers growing nearby. Consequently, pollen collected by both bee species also contained a wide range of pesticides, notably including the fungicides **carbendazim**, boscalid, **flusilazole**, **metconazole**, **tebuconazole** and **trifloxystrobin** and the neonicotinoids **thiamethoxam**, **thiacloprid** and **imidacloprid**. In bumble bees, the fungicides **carbendazim**, boscalid, **tebuconazole**, **flusilazole** and **metconazole** were present at concentrations up to 73 nanogram/gram (ng/g). It is notable that pollen collected by bumble bees in rural areas contained high levels of the neonicotinoids **thiamethoxam** (mean 18 ng/g) and **thiacloprid** (mean 2.9 ng/g), along with a range of fungicides, some of which are known to act synergistically with neonicotinoids. Pesticide exposure of bumble bee colonies in urban areas was much lower than in rural areas. Understanding the effects of simultaneous exposure of bees to complex mixtures of pesticides remains a major challenge.

PMID:26760714
David A et al; Environ Int 88: 169-78 (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

14.2.14 Probable Routes of Human Exposure

Occupational exposure to boscalid may occur through inhalation and dermal contact with this compound at workplaces where boscalid is produced or used. Monitoring data indicate that the general population may be exposed to boscalid via ingestion of some fruits and wines, dermal contact with spray in the vicinity of farms applying boscalid and contact with contaminated surface **water** or sediments in agricultural regions using this fungicide. (SRC)

▸ **Hazardous Substances Data Bank (HSDB)**

Concerns about pesticide drift from neighbouring vineyards affecting children attending school on a farm adjacent to an urban suburb of Cape Town, Western Cape in South Africa were investigated. The study involved a before-after design, measuring levels of environmental exposure before and during pesticide application activities on the neighbouring farms. Samples were collected in air, dust and grass cuttings at the preschool and primary school located on the farms during September-December in 2010 and tested for pesticides using multi-pesticide methods. Eleven different pesticides were detected in the various samples. Six of these chemicals (**endosulfan**, **dimethomorph**, **penconazole**, **cyprodinil**, boscalid and **bromopropylate**) were on the spraying schedules of the two farms neighbouring the schools and the timing and location of detection were generally consistent with farm application. Three pesticides detected (**chlorpyrifos**, **cypermethrin**, **permethrin**) are agents commonly used in household applications and one (**pyriproxifen**) is used in pet treatment agents. **Kresoxim-methyl**, the other pesticide detected, is likely to come from drift from other farms in the area. The concentration of pesticides was all lower than 0.1 ug/cu m in air and 0.1 ug/kg in dust and grass apart from **permethrin** and **cypermethrin**. The findings confirm the presence of drift onto the school premises and concentrations found in this study were generally low in comparison to that detected in other studies. Regular monitoring to track the effectiveness of containment and mitigation measures that reduce drift is recommended.

PMID:23995259

Dalvie MA et al; Sci Total Environ 1: 466-67 (2014)

Hazardous Substances Data Bank (HSDB)

15 Associated Disorders and Diseases

- Comparative Toxicogenomics Database (CTD)

- Therapeutic Target Database (TTD)

16 Literature

16.1 NLM Curated PubMed Citations

PubChem

16.2 Springer Nature References

- Springer Nature

16.3 Thieme References

- Thieme Chemistry

16.4 Wiley References

- Wiley

16.5 Depositor Provided PubMed Citations

- PubChem

16.6 Metabolite References

- Human Metabolome Database (HMDB)

16.7 Chemical Co-Occurrences in Literature

- PubChem

16.8 Chemical-Gene Co-Occurrences in Literature

PubChem

16.9 Chemical-Disease Co-Occurrences in Literature

PubChem

17 Patents

17.1 Depositor-Supplied Patent Identifiers

PubChem

Link to all deposited patent identifiers

PubChem

17.2 WIPO PATENTSCOPE

Patents are available for this chemical structure:

https://patentscope.wipo.int/search/en/result.jsf?inchikey=WYEMLYFITZORAB-UHFFFAOYSA-N

PATENTSCOPE (WIPO)

18 Interactions and Pathways

18.1 Chemical-Target Interactions

- Comparative Toxicogenomics Database (CTD); Toxin and Toxin Target Database (T3DB)

19 Biological Test Results

19.1 BioAssay Results

PubChem

20 Taxonomy

- KNApSAcK Species-Metabolite Database; LOTUS - the natural products occurrence database

21 Classification

21.1 MeSH Tree

Medical Subject Headings (MeSH)

21.2 ChEBI Ontology

ChEBI

21.3 KEGG: Pesticides

KEGG

21.4 ChemIDplus

- ChemIDplus

21.5 UN GHS Classification

- UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

21.6 EPA CPDat Classification

- EPA Chemical and Products Database (CPDat)

21.7 NORMAN Suspect List Exchange Classification

- NORMAN Suspect List Exchange

21.8 CCSBase Classification

- CCSbase

21.9 EPA DSSTox Classification

- EPA DSSTox

21.10 Consumer Product Information Database Classification

- Consumer Product Information Database (CPID)

21.11 LOTUS Tree

- LOTUS - the natural products occurrence database

21.12 FDA Drug Type and Pharmacologic Classification

National Drug Code (NDC) Directory

21.13 EPA Substance Registry Services Tree

EPA Substance Registry Services

22 Information Sources

FILTER BY SOURCE ALL SOURCES

1. **Athena Minerals**

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   https://commonchemistry.cas.org/detail?cas_rn=188425-85-6

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   Boscalid [ISO]
   https://pubchem.ncbi.nlm.nih.gov/substance/?source=chemidplus&sourceid=0188425856

   ChemIDplus Chemical Information Classification
   https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

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   Boscalid
   https://www.drugbank.ca/drugs/DB12792

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   Boscalid
   https://comptox.epa.gov/dashboard/DTXSID6034392

   CompTox Chemicals Dashboard Chemical Lists
   https://comptox.epa.gov/dashboard/chemical-lists/

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3-Pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)
https://echa.europa.eu/substance-information/-/substanceinfo/100.115.343

Boscalid (formerly Nicobifen)
https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/44859

7. FDA Global Substance Registration System (GSRS)

BOSCALID
https://gsrs.ncats.nih.gov/ginas/app/beta/substances/32MS8ZRD1V

8. Hazardous Substances Data Bank (HSDB)

BOSCALID
https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7499

9. CCSbase

Boscalid

CCSbase Classification
https://ccsbase.net/

10. NORMAN Suspect List Exchange

Boscalid

NORMAN Suspect List Exchange Classification
https://www.norman-network.com/nds/SLE/

11. ChEBI

Boscalid
http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:81822

ChEBI Ontology
http://www.ebi.ac.uk/chebi/userManualForward.do#ChEBI%20Ontology

12. LOTUS - the natural products occurrence database

Boscalid
https://www.wikidata.org/wiki/Q894358

LOTUS Tree
https://lotus.naturalproducts.net/

13. ## Toxin and Toxin Target Database (T3DB)

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> http://www.t3db.ca/downloads

Boscalid
http://www.t3db.ca/toxins/T3D3800

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15. ## Comparative Toxicogenomics Database (CTD)

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2-chloro-N-(4-chlorobiphenyl-2-yl)nicotinamide
https://ctdbase.org/detail.go?type=chem&acc=C550088

16. ## Therapeutic Target Database (TTD)

Boscalid
https://idrblab.net/ttd/data/drug/details/D0R4EY

17. ## Consumer Product Information Database (CPID)

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>
> https://www.whatsinproducts.com/contents/view/1/6

Boscalid
https://www.whatsinproducts.com/chemicals/view/1/5008/188425-85-6

Consumer Products Category Classification
https://www.whatsinproducts.com/

18. ## EPA Chemical and Products Database (CPDat)

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> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

https://comptox.epa.gov/dashboard/DTXSID6034392#exposure

EPA CPDat Classification
https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

19. ## Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

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>
> https://haz-map.com/About

Boscalid
https://haz-map.com/Agents/3988

20. ## EPA Pesticide Ecotoxicity Database

> LICENSE
> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

https://ecotox.ipmcenters.org/

21. ## EU Pesticides Database

Boscalid (formerly nicobifen)
https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event=as.details&as_id=472

22. ## Human Metabolome Database (HMDB)

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> http://www.hmdb.ca/citing

Boscalid
http://www.hmdb.ca/metabolites/HMDB0249353

HMDB0249353_msms_2226978
https://hmdb.ca/metabolites/HMDB0249353#spectra

23. ## Japan Chemical Substance Dictionary (Nikkaji)

http://jglobal.jst.go.jp/en/redirect?Nikkaji_No=J1.989.940C

24. ## KNApSAcK Species-Metabolite Database

Boscalid
http://www.knapsackfamily.com/knapsack_core/info.php?sname=C_ID&word=C00060571

25. ## Kruve Lab, Ionization & Mass Spectrometry, Stockholm University

boscalid

26. ## MassBank Europe

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> https://github.com/MassBank/MassBank-web/blob/main/MassBank-Project/LICENSE.txt

WYEMLYFITZORAB-UHFFFAOYSA-N
https://massbank.eu/MassBank/Result.jsp?inchikey=WYEMLYFITZORAB-UHFFFAOYSA-N

27. ## MassBank of North America (MoNA)

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> https://mona.fiehnlab.ucdavis.edu/documentation/license

Boscalid
https://mona.fiehnlab.ucdavis.edu/spectra/browse?query=exists(compound.metaData.name:%27InChIKey%27%20and%20compound.metaData.value:%27WYEMLYFITZORAB-UHFFFAOYSA-N%27)

28. ## Metabolomics Workbench

Boscalid
https://www.metabolomicsworkbench.org/data/StructureData.php?RegNo=153713

29. ## National Drug Code (NDC) Directory

EMERALD
https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory

30. ## NIST Mass Spectrometry Data Center

BOSCALID
http://www.nist.gov/srd/nist1a.cfm

31. ## SpectraBase

Boscalid
https://spectrabase.com/spectrum/KCCDJ3TY9y0

Boscalid
https://spectrabase.com/spectrum/5QGEVjzhDBA

32. ## Springer Nature

https://pubchem.ncbi.nlm.nih.gov/substance/?source=15745&sourceid=23053073-915577709

33. ## Thieme Chemistry

https://pubchem.ncbi.nlm.nih.gov/substance/?source=22163&sourceid=23053073-915577709

34. ## USDA Pesticide Data Program

Boscalid
https://www.ams.usda.gov/datasets/pdp/pdpdata

35. ## Wikidata

boscalid
https://www.wikidata.org/wiki/Q894358

36. ## Wikipedia

boscalid
https://en.wikipedia.org/wiki/Succinate_dehydrogenase

Emerald
https://en.wikipedia.org/wiki/Emerald

37. ## Wiley

https://pubchem.ncbi.nlm.nih.gov/substance/?source=wiley&sourceid=67543

38. ## PubChem

https://pubchem.ncbi.nlm.nih.gov

39. ## Medical Subject Headings (MeSH)

2-chloro-N-(4-chlorobiphenyl-2-yl)nicotinamide
https://www.ncbi.nlm.nih.gov/mesh/67550088

MeSH Tree
http://www.nlm.nih.gov/mesh/meshhome.html

40. ## KEGG

Pesticides
http://www.genome.jp/kegg-bin/get_htext?br08007.keg

41. ## UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

GHS Classification Tree
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

42. ## EPA Substance Registry Services

EPA SRS List Classification
https://sor.epa.gov/sor_internet/registry/substreg/LandingPage.do

43. ## PATENTSCOPE (WIPO)

SID 389366395
https://pubchem.ncbi.nlm.nih.gov/substance/389366395

44. ## NCBI

https://www.ncbi.nlm.nih.gov/projects/linkout

Attachment C

USEPA Office of Chemical Safety and Pollution Prevention Memorandum
Boscalid. Human Health Risk Assessment for Registration Review

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: **09/25/2019**

SUBJECT: **Boscalid**. Human Health Risk Assessment for Registration Review.

PC Code: 128008
Decision No.: 549965
Petition No.: NA
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: **NA**
MRID No.: **NA**

DP Barcode: D451675
Registration Nos.: See Use Profile Appendix E
Regulatory Action: Registration Review
Case No.: NA
CAS No.: 188425-85-6
40 CFR: §180.589

FROM: Johnnie L Smith II, Chemist/Risk Assessor
Meheret Negussie, Chemist
Myron S. Ottley, Ph.D., Senior Biologist
Seyed Tadayon, Chemist
Risk Assessment Branch III (RAB 3)
Health Effects Division (HED, 7509P)

THROUGH: Thomas Moriarty, Branch Chief
RAB 3/HED (7509P)

TO: Jordan Page, Chemical Review Manager
Jill Bloom, Team Leader
Risk Management and Implementation Branch 5
Pesticide Re-Evaluation Division (PRD, 7508P)

As part of Registration Review, PRD of the Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of boscalid. This memorandum serves as HED's human health risk assessment of the dietary, occupational, and residential exposure; and aggregate risk from the registered uses of boscalid. The most recent risk assessment for boscalid was conducted in 2018 (L. Bacon, D440500, 05/30/2018). A summary of the findings and an assessment of human risk resulting from the registered uses of boscalid are provided in this document.

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1.0 Executive Summary

Boscalid, 2-chloro-*N*-(4′-chloro[1,1′-biphenyl]-2-yl)-3-pyridinecarboxamide, is a carboxamide (anilide) class fungicide that inhibits mitochondrial respiration, thereby inhibiting spore germination, germ tube elongation, mycelial growth, and sporulation in all major stages of fungal development and reproduction necessary for disease development. Boscalid is registered for use on numerous agricultural food crops, as well as on golf course turf grass, residential ornamentals and landscape gardens.

HED has made the following updates for the boscalid registration review

- Hazard profile has been updated to be consistent with current practices;
- An inhalation toxicity study has been received, reviewed and incorporated into the boscalid hazard profile;
- The Uncertainty Factors for boscalid have been updated, based upon the receipt of an acceptable inhalation toxicity study;
- Chemical specific dislodgeable foliar residue data have been reviewed and incorporated into this boscalid draft risk assessment.

Use Profile

Boscalid is currently registered for use on numerous agricultural and orchard crops, and as a seed treatment, on golf course turf, residential ornamentals, landscape gardens, residential fruit and nut trees, and greenhouse grown tomato transplants for the home consumer market. The registered seed treatment uses are commercial only and the use of on-farm seed treatment is prohibited. Boscalid end use products are formulated as emulsifiable concentrates, flowable concentrates, soluble concentrates, soluble concentrate/solid, water dispersible granules, and ready-to-use solutions. Applications can be made with ground, aerial, airblast, chemigation, hand held, or seed treatment equipment. The registered seed treatment uses are commercial only and the use of on-farm seed treatment is prohibited.

The majority, but not all, of occupational labels require baseline personal protective equipment (PPE), consisting of single layer clothing (long sleeve shirt, long pants, socks and shoes), and chemical resistant gloves. Some, but not all, labels also require the use of additional PPE such as protective eye wear and NIOSH filtering half-face respirators. The restricted entry interval (REI) on the registered labels is 12 hours.

Exposure Profile

Humans may be exposed to boscalid in food and drinking water since boscalid may be applied directly to growing crops and following harvest, and application may result in boscalid reaching surface and ground sources of drinking water. In an occupational setting, applicators may be exposed while handling the pesticide prior to application as well as during application. There is also potential for post-application exposure for workers re-entering treated fields. In a residential setting, all registered boscalid product labels with residential use sites (e.g., garden and trees) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use personal protective equipment (PPE). Therefore, HED has made the assumption that these products are not for homeowner use and has not conducted a quantitative residential handler assessment. Adults and children may be exposed to residues on treated foliage following

application of boscalid in residential and similar settings. Non-occupational exposure resulting from spray drift from agricultural applications onto residential areas may also occur.

Hazard Characterization
The boscalid toxicity database is complete, and there are no reproductive, developmental, immunotoxic or neurotoxic concerns. In mammals, the primary targets are the liver and the thyroid (indirectly from liver adaptive response). In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased body weights and effects on the liver and, thyroid effects seen in rats and dogs. Mode of action studies conducted in rats indicated that boscalid has a direct effect upon the liver and that the thyroid effects are secondary to the liver effects. The oral (chronic dietary and incidental oral), dermal and inhalation endpoints are based on two co-critical studies: the chronic toxicity rat and carcinogenicity rat, based on thyroid effects. A dermal absorption of 15% was used for the exposure assessment. Since inhalation absorption data are not available, toxicity by the inhalation route is considered to be equivalent to the estimated toxicity by the oral route of exposure. The Food Quality Protection Act (FQPA) safety factor (SF) for boscalid has been reduced to 1X because points of departure (PODs) selected for risk assessment are protective of all adverse effects observed in offspring and there are no residual uncertainties regarding pre- or postnatal susceptibility. The Cancer Assessment Review Committee (CARC) has classified boscalid as "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential," and the quantification of human cancer risk is not recommended (J. Kidwell, TXR 0051289, 11/14/2002) The RfD approach would be protective of both chronic toxicity and carcinogenic potential of this chemical. The level of concern (LOC) for all exposure scenarios is a margin of exposure (MOE) <100. Oral, dermal and inhalation risk estimates may be combined, as appropriate, in this assessment because the points of departure (PODs) are based on the same toxicological studies and the effects for these exposure routes are the same.

Dietary Exposure Assessment
As there were no observed effects attributable to a single dose, an acute endpoint was not established. Therefore, an acute dietary exposure assessment was not conducted. The chronic dietary (food and drinking water) risk estimates are 20% of the chronic population adjusted dose (cPAD) for the general U.S. population and 57% of the cPAD for all infants (<1 year old), the most highly exposed population subgroup. The chronic dietary exposure estimates for food and drinking water are not of concern (<100% cPAD).

A cancer dietary assessment was not conducted since boscalid was classified by the Cancer Assessment Review Committee (CARC) as "suggestive evidence of carcinogenicity"; quantification of human cancer risk is not recommended (J. Kidwell, TXR 0051289, 11/14/2002).

Residential Exposure and Risk Assessment
All registered boscalid product labels with residential use sites (golf course, garden and trees) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use personal protective equipment (PPE). Therefore, HED has made the assumption that these products are not for homeowner use and has not conducted a quantitative residential handler assessment.

None of the residential post-application exposures resulted in dermal risk estimates of concern. Dermal margins of exposure (MOEs) for adults, children 6 to <11 years old and youth 11 < 16 years old ranged from 190-12,000 (LOC = 100).

Aggregate Risk Assessment
There is potential for short-term aggregate exposure to boscalid via dietary (which is considered background exposure) and residential (which is considered primary) exposure pathways. The aggregate MOEs are 170 for children 6 to 11 years old, 650 for youth 11 to 16 years old, and 140 for adults (LOC = 100). None of these aggregate risk estimates are of concern to HED.

Occupational Exposure and Risk Assessment
The majority of the occupational handler dermal, inhalation and combined risk estimates did not result in risk estimates of concern (MOEs ≥ 100) with baseline attire. Only one scenario, mixer/loader of a dry flowable (DF) formulation for aerial application to high-acreage field crops, resulted in MOEs less than the LOC at baseline attire (Dermal MOE = 89; Total Dermal plus Inhalation MOE = 71). This scenario is not of concern with the addition of gloves (Dermal MOE = 390; Total Dermal plus Inhalation MOE = 180), which are required in the DF label PPE statement.

Chemical specific dislodgeable foliar residue (DFR) data was available and employed to assess potential post-application exposure and risks for boscalid. Most of the dermal post-application exposure scenarios resulted in MOEs greater than the LOC (MOE ≥ 100) on day 0 and are not of concern. The only risk estimates of concern on day 0 (MOE < 100) were for girdling and turning grapes up to 22 days after applications at 0.362 lb ai/A (employing grape DFR data). Other than grape girdling activity, all post-application scenarios resulted in dermal MOEs greater than the LOC of 100 on Day 0 (12 hours after application). where MOEs (except for grape, tying and turning) ranged from 100 – 22,000. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for boscalid at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for boscalid.

Spray Drift Risk Assessment
A quantitative spray drift assessment for boscalid was conducted. For adults (dermal) and children 1 to <2 years old (combined dermal and incidental oral), risk estimates are acceptable at the edge of the field (i.e., MOEs ≥ 100). The MOEs range 800 to 3,200 at the edge of the field (i.e., MOEs ≥ 100).

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. **Appendix C** provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied see Appendix C).

2.0 Risk Assessment Conclusions

There are no dietary risks of concern or residue chemistry deficiencies. There are no residential risk estimates of concern. However, there is an occupational dermal post-application exposure risk estimate of concern (MOE < 100) on day zero for girdling and turning grapes up to 22 days after applications at 0.362 lb ai/A.

The specific tolerance recommendations are discussed in Table 2.2.2.

2.1 Data Deficiencies

Previously Identified Data Gap

870.3465 Subchronic Inhalation study: In the last risk assessment, the toxicity database for boscalid was considered adequate for risk assessment, except for a subchronic inhalation study. HED had recommended requiring the subchronic inhalation study (K. Rury, TXR 0056585, 03/07/2013), which was subsequently required through the registration review Generic Data Call-in for boscalid. This study has been submitted and reviewed, and the toxicity database is considered to be complete at this time.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) method (BASF Method D9908, Version II) is available for enforcing tolerances for boscalid in/on plant commodities. Briefly, the residues are extracted from plant commodities, with methanol (MeOH): water: 2 N HCl (70:25:5; v/v/v) and centrifuged. Residues from each commodity were then diluted with 1N HCl saturated with NaCl and partitioned into cyclohexane. Residues were concentrated to dryness, re-dissolved in MeOH: water: 4 mM ammonium formate (80:20:0.1, v/v/v), and analyzed using LC/MS/MS using the *m/z* 343→307 ion transition to detect and quantify boscalid. Residues are quantified using an external calibration curve of boscalid standards. The validated level of quantitation (LOQ) (LLMV, lower limit of method validation) was 0.05 ppm.

2.2.2 Recommended & Established Tolerances

The residue definition (40 CFR §180.589) complies with the recommendation of the S. Knizner 05/27/2009 memo. No changes to the tolerance expression are required. During Registration Review, tolerance updates are being recommended in accordance with HED's standard practice and policies. Some tolerances have been corrected to reflect the appropriate rounding classes, commodity definitions and harmonization.

Table 2.2.2. Tolerance Summary for Boscalid—Recommended Changes.

Commodity/Correct Commodity Definition	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
40CFR 180.589 (a) General (1)			
Almond, hulls	17	15	Harmonization with Codex
Avocado	1.5	**2**	Harmonization with Canada
Banana[1]	**--**	**0.6**	Commodity definition correction/Harmonization with Codex
Banana, import[1]	0.40	**--**	
Coffee, green bean[1]	**--**	**0.05**	Commodity definition correction
Coffee, green bean, import[1]	0.05	--	
Endive, Belgian	**--**	**6**	Commodity definition correction/ Corrected value to be consistent with HED Rounding Class Practice
Endive, Belgium	6.0	--	
Fennel, florence, fresh leaves and stalk	--	**45**	Commodity definition correction
Fennel, Florence	45	--	
Fruit, citrus, group 10-10, dried pulp	**--**	**4.5**	Commodity definition correction
Citrus, dried pulp	4.5	--	
Fruit, citrus, group 10-10, oil	--	**85**	Commodity definition correction
Citrus, oil	85.0	--	
Fruit, stone, group 12-12	3.5	**5**	Harmonization with Codex
Mango	1.5	**2**	Harmonization with Canada
Papaya	1.5	**2**	
Peppermint, fresh leaves	**--**	**30**	Commodity definition correction/ Corrected value to be consistent with HED Rounding Class Practice
Peppermint, tops	30.0	--	
Rapeseed subgroup 20A, oil	**--**	**5**	Commodity definition correction/ Corrected value to be consistent with HED Rounding Class Practice
Canola, refined oil	5.0	--	
Spearmint, leaves	**--**	**30**	Commodity definition correction/ Corrected value to be consistent with HED Rounding Class Practice
Spearmint, tops	30.0	--	
Vegetable, legume, dried shelled, except soybean, subgroup 6C	--	**3**	Commodity definition correction/Harmonization with Codex
Pea and bean, dried shelled, except soybean, subgroup 6C	2.5	**--**	
Vegetable, legume, edible podded, subgroup 6A	--	**5**	Commodity definition correction/Corrected value to be

Table 2.2.2. Tolerance Summary for Boscalid—Recommended Changes.			
Commodity/Correct Commodity Definition	**Established Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments**
Vegetable, legume, edible podded subgroup 6A	5.0	--	consistent with HED Rounding Class Practice
Vegetable, legume, succulent shelled, subgroup 6B	--	**0.6**	Commodity definition correction/Corrected value to be consistent with HED Rounding Class Practice
Pea and bean, succulent shelled, subgroup 6B	0.60	--	
40CFR 180.589 (a) General (2)			
Hog, fat	0.20	0.3	Harmonization with Canada
Hog, meat	0.05	0.01	
Hog, meat byproducts	0.10	0.35	
Tolerance Revisions for Significant Figures			
40CFR 180.589 (a) General (1)			
Alfalfa, forage	30.0	30	Corrected value to be consistent with HED Rounding Class Practice
Alfalfa, hay	65.0	65	
Artichoke, globe	6.0	6	
Bushberry subgroup 13-07B	13.0	13	
Caneberry subgroup 13-07A	10.0	10	
Cotton, gin byproducts	55.0	55	
Fruit, citrus, group 10-10	2.0	2	
Fruit, pome, group 11-10	3.0	3	
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	5.0	5	
Grain, aspirated fractions	3.0	3	
Kohlrabi	6.0	6	
Nut, tree, group 14-12	0.70	0.7	
Persimmon	8.0	8	
Soybean, vegetable	2.0	2	
Star apple	8.0	8	
Vegetable, root, except sugar beet, subgroup 1B	2.0	2	
40CFR 180.589 (a) General (2)			
Cattle, fat	0.30	0.3	Corrected value to be consistent with HED Rounding Class Practice
Cattle, meat	0.10	0.1	
Goat, fat	0.30	0.3	
Goat, meat	0.10	0.1	
Horse, fat	0.30	0.3	
Horse, meat	0.10	0.1	
Milk	0.10	0.1	
Poultry, fat	0.20	0.2	
Poultry, meat byproducts	0.20	0.2	
Sheep, fat	0.30	0.3	

Table 2.2.2. Tolerance Summary for Boscalid—Recommended Changes.			
Commodity/Correct Commodity Definition	**Established Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments**
Sheep, meat	0.10	0.1	
40CFR 180.589 (d)			
Animal feed, nongrass, group 18, forage, except alfalfa	1.0	1	Corrected value to be consistent with HED Rounding Class Practice
Animal feed, nongrass, group 18, hay, except alfalfa	2.0	2	
Grain, cereal, forage, fodder, and straw, group 16, forage	**--**	**2**	
Grain, cereal, forage, fodder and straw, group 16, forage	2.0	--	
Grain, cereal, forage, fodder, and straw, group 16, straw	**--**	**3**	
Grain, cereal, forage, fodder and straw, group 16, straw	3.0	--	
Grain, cereal, group 15	0.20	0.2	
Grass, forage, fodder, and hay, group 17, forage	**--**	**2**	
Grass, forage, fodder, and hay, group 17, forage	2.0	--	
Grass, forage, fodder, and hay, group 17, hay	**--**	**8**	
Grass, forage, fodder, and hay, group 17, hay	8.0	--	
Grass, forage, fodder, and hay, group 17, seed screenings	**--**	**0.2**	
Grass, forage, fodder, and hay, group 17, seed screenings	0.20	--	
Grass, forage, fodder, and hay, group 17, straw	**--**	**0.3**	
Grass, forage, fodder, and hay, group 17, straw	0.30	--	
Rice, hulls	0.50	0.5	
Vegetable, foliage of legume, group 7, hay	2.0	2	
Vegetable, leafy, except brassica, group 4, except celery, lettuce, and spinach	1.0	Revoke	

[1] No US registration as of September 16, 2009

2.2.3 International Harmonization

The boscalid tolerance definition in the United States (US), Codex, and Canada is parent boscalid for plant commodities. The US and Canadian residue definitions for livestock commodities are parent plus the metabolite (CCIM), but Codex includes parent boscalid only.

Codex has established maximum residue limits (MRLs) on residues of boscalid for several plant and livestock commodities. The US tolerances for residues on caneberry subgroup 13-07A,

coffee, citrus fruit, small fruit vine climbing 13-07F, bulb vegetables, cucurbit vegetables, fruiting vegetables, and root vegetables, egg, and milk are harmonized with the Codex MRLs.

HED believes that the following commodities are eligible for harmonization with Codex MRLs; these tolerances are currently not harmonized with Canadian MRLs (except legume vegetables subgroup 6C) or there are no Canadian MRLs: almond hulls, banana (import), legume vegetables subgroup 6C, and stone fruit.

HED believes that the following commodities are not eligible for harmonization with Codex because of the large difference between the US tolerance and the Codex MRL values: globe artichoke, Belgium endive, succulent shelled peas and beans, straw of cereal grains group 16, and leaves of root and tuber group 2.

HED believes that the following commodities are eligible for harmonization with Codex MRLs; these tolerances are currently harmonized with Canadian MRLs and the Agency will consider input from stakeholders regarding harmonization preferences (in the context of reducing trade irritants), low growing berries subgroup 13-07G, tree nuts, and peanuts.

Overall, US and Canadian tolerances/MRLs are harmonized for some plant commodities and the majority of livestock commodities (except hog commodities and some poultry commodities).

The US tolerances are greater than the Canadian MRLs for *Brassica* leafy greens subgroup 4-16B, bushberry subgroup 13-07B, caneberry subgroup 13-07A, small fruit vine climbing subgroup 13-07F, stone fruits, leafy greens subgroup 4-16A, oilseed group 20 (for 20B and C), bulb vegetables, cucurbit vegetables, fruiting vegetables, root vegetable subgroup 1B, poultry fat, and poultry meat byproducts.

The US tolerances are less than the Canadian MRLs for avocado, mango, papaya, and hog (fat, meat, and meat byproducts). HED is recommending increasing these tolerances for harmonization purposes.

For a complete summary of U.S. tolerances and Canadian and Codex MRLs for plant and livestock commodities, refer to Appendix D.

2.3 Label Recommendations

There are risk estimates of concern related to girdling and turning grapes up to 22 days after applications at 0.362 lb ai/A.

2.3.1 Recommendations from Residue Reviews

None

2.3.2 Recommendations from Residential Assessment

None

2.3.3 Recommendations from Occupational Assessment

None

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature of boscalid are presented in Appendix B, Table B-1.

3.2 Physical/Chemical Characteristics

The physicochemical properties of the technical grade of boscalid are presented in Appendix B, Table B-2.

3.3 Pesticide Use Pattern

The summary of directions for agricultural occupational and residential uses of boscalid are presented in Appendix E, Tables E-1 and E-2.

3.4 Anticipated Exposure Pathways

Humans may be exposed to boscalid in food and drinking water, since boscalid may be applied directly to growing crops and seeds, and application may result in boscalid reaching surface and ground water sources of drinking water. Additionally, there are residential uses of boscalid that may result in post-application exposures for adults and children. In an occupational setting, mixers, loaders, and applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

This risk assessment considers all of the aforementioned exposure pathways based all existing uses.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a

pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it is also being was considered whenever appropriate in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

The Agency reassessed the toxicity databases for boscalid in accordance with current policies and determined that many of the effects previously noted are no longer considered to be adverse, It should be noted that many of the no observed adverse effect levels (NOAELs) and lowest observed affect levels (LOAELs) presented in the toxicology profile table (Appendix A) have not been updated to comply with current policy since they did not impact points of departure for risk assessment.

4.1 Toxicology Studies Available for Analysis

The available toxicity studies include:

- acute toxicity battery,
- oral subchronic studies (rat, mouse and dog),
- dermal subchronic study (rat),
- inhalation subchronic study (rat),
- oral developmental (rat, rabbit), reproductive (rat) studies
- neurotoxicity battery (rat, acute and subchronic)
- immunotoxicity (rat) study,
- oral chronic (rat, dog) and carcinogenicity (rat, mouse) studies,
- mutagenicity battery,
- metabolism and pharmacokinetics studies (rat), and
- special oral subchronic (rat) studies on hepatic enzyme induction, thyroid hormone induction and reversibility of these inductions.

In the last risk assessment, the toxicity database for boscalid was considered adequate for risk assessment, except for the absence of a subchronic inhalation study. HED had recommended that the subchronic inhalation study be required (K. Rury, TXR 0056585, 03/07/2013). This study has been submitted, reviewed (V. Chen, TXR 0057749, 06/22/2018), and summarized in Section A.3. This data gap has been filled and the toxicity database is complete. As a result, the 10X database uncertainty factor applied to inhalation risk assessments has been removed. Also, the endpoint and point of departure for the co-critical studies used for risk assessment have been updated according to current evaluation practices, and these changes are detailed in Section 4.5 of this document.

As part of registration review for boscalid, a broad survey of the literature was conducted to identify studies that report toxicity following exposure to boscalid via exposure routes relevant to human health pesticide risk assessment not accounted for in the agency's boscalid toxicology database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 29 studies from the literature. During the title/abstract and/or full text screening of these studies, none of the studies were deemed to contain potentially relevant information (either quantitative or qualitative) for the boscalid human health risk assessment. Appendix A.4 has additional information regarding the literature review.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

In metabolism and kinetics studies, boscalid was absorbed to some degree, 17% in the low dose (50 mg/kg/day) and 3.5% at 500 mg/kg/day. These values were increased approximately three-fold when biliary excretion data were incorporated. The lower percentages of high-dose absorption were considered to be due to saturation, which was supported by the decreased urinary and biliary excretion, and greater fecal excretion observed in the high-dose group. There did not appear to be any biologically relevant differences in the total absorption between the single dose and the 15-day repeated dose regimens nor were there any remarkable gender-related differences. Maximum plasma concentration (T_{max}) was achieved in 8 hours regardless of dose. Elimination of radioactivity from the plasma appeared to be biphasic with a rapid decline from T_{max} to 24 hours ($t_{1/2}$~8.1 hr) followed by a slower elimination phase ($t_{1/2}$~29.9 hr). There did not appear to be biologically significant gender-related differences in pharmacokinetic parameters. The area under the curve (AUC) values and maximum plasma concentrations did not reflect the 10-fold difference in administered dose.

Tissue distribution data showed that radioactivity was most prevalent in organs/tissues associated with absorption, metabolism and elimination processes such as liver, kidneys, gut and adipose tissue. Tissue burdens for the low- and high-dose groups did not, however, reflect the 10-fold difference in dose. Radioactivity in the thyroid and bone marrow appeared to be greatest at the 168–hour time point. The metabolite characterization findings were consistent with Phase I oxidation followed by Phase II conjugation processes. The most prominent metabolites in the urine, bile and liver were M510F01 (a hydroxylation product) and M510F02 (a glucuronide conjugate). In the feces, parent compound (representing unabsorbed material) was the most prevalent component.

Excretion of administered radioactivity was primarily via the feces (~80-98%) for all treatment groups regardless of dose level or label position. Urinary excretion accounted for the majority of the remainder of the radiolabel. Although excretion profiles were similar for the single high-dose and repeat high-dose groups, somewhat greater urinary excretion of radioactivity was observed for the low-dose group. Biliary excretion represented approximately 40 to 50% of the fecal radioactivity in the low-dose group but only about 10% in high-dose group. This was also confirmed by the plasma kinetics and AUC data. Excretory patterns did not significantly differ by gender or position of the radiolabel.

4.2.1 Dermal Absorption

Based on the results of an available *in vivo* dermal absorption study in rats the dermal absorption factor (DAF) of boscalid is determined to be 15%, as represented by 11% being absorbed plus 4% found as bound residue on the skin following a 24 hr exposure.

4.3 Toxicological Effects

Boscalid is a carboxamide (anilide) fungicide that acts in the fungal cell by inhibiting mitochondrial respiration and subsequent production of adenosine triphosphate (ATP) and by inhibiting the succinate-ubiquinone oxidase reductase system in Complex II of the mitochondrial electron transport chain.

In mammals, the target organs are the liver and the thyroid (indirectly from liver adaptive response). In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased body weights (primarily in mice) and effects on the liver (increase in weights, changes in enzyme levels and histopathological changes) as well as on the thyroid (increase in weights (rats and dogs) and histopathological changes (rats)). Mode of action studies conducted in rats indicated that boscalid has a direct effect upon the liver and that the thyroid effects are secondary. A reversibility study in rats indicated that both liver and thyroid parameters returned to control values after the animals were placed on control diet. Absolute and/or relative thyroid weights were elevated in rats and dogs, but there were no histopathological changes observed in the thyroid in either mice or dogs.

In a developmental toxicity study in rats, no developmental toxicity was observed in the fetuses at the highest dose tested (limit dose). No effects were noted in the dams in this study. In a developmental toxicity study in rabbits, an increased incidence of abortions or early delivery was observed at the limit dose. There was quantitative evidence of increased susceptibility in the two-generation reproduction study in rats, where decreases in body weights in male offspring were seen at a dose that was lower than the dose that induced parental/systemic toxicity. There was quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats, where decreases in pup body weights on post-natal day four (PND 4) and body weight gains (PND 1-4) were seen in the absence of any maternal toxicity.

In a two-year chronic toxicity study and a two-year carcinogenicity study in male and female rats, the combined data showed an increased trend in thyroid follicular cell adenomas in males. This was supported by thyroid hypertrophy and hyperplasia of follicular cells at the same dose as well as increased thyroid weights plus mechanistic data. The mouse carcinogenicity study was negative. Boscalid was negative in the mutagenicity battery.

There was no evidence of neurotoxicity in rats in the acute, subchronic or developmental studies up to the limit dose. No neurotoxic observations were noted in any of the other studies in any species. Similarly, there was no evidence of immunotoxicity in the available immunotoxicity study in rats, or in any of the other studies in the database.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[2]

The toxicity database for boscalid is considered adequate for risk assessment. There was no evidence of neurotoxicity in the database; there is low or no concern for developmental or reproductive toxicity, and for susceptibility in the developing or young animal. There are no residual uncertainties identified in the exposure databases. Therefore, the FQPA Safety Factor has been reduced to 1X.

4.4.1 Completeness of the Toxicology Database

The toxicity database is considered complete and adequate for risk assessment. All studies needed to assess susceptibility concerns, such as developmental and reproduction studies, have been submitted. Additional studies, such a developmental neurotoxicity study, acute and subchronic neurotoxicity studies and an immunotoxicity study are also available.

4.4.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity based on an acute neurotoxicity study, a 90-day neurotoxicity study and a developmental neurotoxicity study (all in rats). There was no evidence of neurotoxicity in the other subchronic and chronic studies in the toxicity database.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no evidence of either quantitative or qualitative susceptibility observed in the pre-natal developmental toxicity studies in rats and rabbits. In the rat, no maternal or fetal toxicity was seen up to the limit dose, and in rabbits, abortions and/or early delivery was the only affect observed, which could be considered as either a maternal or fetal effect, brought on by maternal stress. Therefore, there are no concerns for pre-natal susceptibility.

Post-natal susceptibility was observed in both the multi-generation reproduction study (in F_2 males and F_1 and F_2 females) and the developmental neurotoxicity study (PND 4 males and females) in the form of decreased pup weights in offspring at dose levels that were non-toxic in parents. The susceptibility seen in the reproduction study was of low concern because the endpoints and PODs used for risk assessment are protective of these effects. The susceptibility seen pups in the DNT study is also of low concern because it was not seen at PND 21 and is considered reversible, and because the PODs used for risk assessment are protective of these effects.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties identified in the exposure databases. The chronic dietary food exposure assessments were performed using conservative approaches including tolerance-level residues, and average percent crop treated (PCT) estimates for existing crops and 100 PCT assumptions. Although some of the residue values used in the dietary exposure assessment were

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

slightly refined, these assessments will not underestimate the exposure and risks posed by boscalid. EPA made conservative (protective) assumptions in the ground and surface water modeling used to assess exposure to boscalid in drinking water. EPA also used conservative assumptions to assess post-application exposure of adults and children. In addition, the residential exposure assessment is based on the updated 2012 Residential SOPs employing surrogate study data, including conservative exposure assumptions based on Day 0 contact to turf and surfaces treated at the maximum application rate. These data are reliable and are not expected to underestimate risks to adults or children. The Residential SOPs are based upon reasonable "worst-case" assumptions and are not expected to underestimate risk.

4.5 Toxicity Endpoint and Point of Departure Selections

The endpoints and points of departure for this risk assessment have been updated for the registration review process and are summarized below.:

Acute dietary endpoints: As there were no toxic effects attributable to a single dose, including in the developmental toxicity studies (late-term abortions seen in the rabbit developmental study were considered multiple-dose effects), an endpoint of concern was not identified to quantify acute-dietary risk to the general population or to the subpopulation females 13-49 years old. The changes in brain morphometrics seen in the developmental neurotoxicity study were not selected as a toxicological endpoint, as they were observed only at a dose exceeding the limit dose (1442 mg/kg/day). Therefore, an acute RfD was not established for any population for boscalid.

Chronic dietary endpoint: Previously (L. Bacon, D440500, 05/30/2018), HED selected the NOAEL of 21.8 mg/kg/day for establishing the chronic dietary, short- and intermediate-term incidental oral, short- and intermediate-term dermal and short- and intermediate-term inhalation PODs, based on the combined results of the following three studies: chronic rat, carcinogenicity rat and 1-year dog. While this NOAEL is higher than the NOAELs in the 90-day study in dogs (7.6 mg/kg/day), the two-generation reproduction study (10.1 mg/kg/day) and the developmental neurotoxicity study (14 mg/kg/day), these differences are considered an artifact of the dose selection process in these studies as shown below. In addition, the values of the LOAELs were centered around 100 mg/kg/day for most of the studies, except the 1-year dog study where the effects at the LOAEL as presented in the table (57 mg/kg/day) are not considered to be adverse based on current evaluation criteria.

Table 4.5. Summary of the Rationales for Endpoints and Points of Departure Selection.

Study	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	LOAEL:NOAEL Ratio	Effects at the LOAEL
90-day – dog	7.6	78.1	10.3	increased alkaline phosphatase activity and hepatic weights in males and females.
90-day – rat	34	137	4.0	M = increases in absolute and relative thyroid weights and increased incidence of thyroid hyperplasia as well as follicular epithelial hypertrophy
2-generation reproduction – rat	10.1	101.6	10.0	Decreased pup weights in F_2 males and F_1 and F_2 females

Table 4.5. Summary of the Rationales for Endpoints and Points of Departure Selection.				
Study	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**	**LOAEL:NOAEL Ratio**	**Effects at the LOAEL**
developmental neurotoxicity – rat	14.0	147	10.5	decreased body weights on PND 4; not observed at PND 21
1-year – dog	**21.8**	**57.4**	2.6	elevated ALP activities and elevated hepatic weights
Chronic – rat	**21.9**	**110**	5.0	Increased thyroid weights and increased incidence of thyroid follicular cell hyperplasia and diffuse follicular cell hypertrophy in males and females
Carcinogenicity – rat	**23.0**	**116**	5.0	Increased incidence of thyroid follicular cell hyperplasia and hypertrophy in males and females

The liver effects seen in the chronic dog study are now considered to be an adaptive response and not adverse based on current toxicology practices; they are no longer appropriate for use in the risk assessment. However, the POD for risk assessment has not changed much because thyroid effects were seen in the rat studies at similar dose levels. The POD for risk assessment is being updated from 21.8 mg/kg/day to 22 mg/kg/day from the long-term rat studies, and the endpoint is now considered the thyroid lesions seen in the subchronic and chronic rat studies at 110 mg/kg/day and above.

Thyroid effects were seen in the rat and dog and after various exposure durations (subchronic and chronic exposures) but were not observed at the LOAELs in either the two-generation reproduction or the developmental neurotoxicity studies. In addition, HED examined the available thyroid toxicity and mechanistic data for boscalid and recommended that a comparative thyroid assay to determine possible susceptibility in the young is not required at this time (H. Pope-Varsalona, TXR 0057878, 06/12/2019). Therefore, there are no residual uncertainties for pre- and post-natal toxicity and the FQPA SF is reduced to 1X. The 10X inter-species safety factor for extrapolation from animal to human and 10X intra-species safety factor are both applied, resulting is a LOC of 100X.

*Occupational and Residential endpoints***:** The incidental oral, dermal and inhalation endpoints (both short- and intermediate-term) are based on the co-critical rat studies. Neither dermal nor systemic toxicity was seen at the limit dose (1000 mg/kg/day) in the 28-day dermal toxicity study in rats. The oral NOAEL of 22 mg/kg/day was selected because of the concerns for the decreases in the body weight and body weight gains seen in the offspring in the two-generation reproduction and the developmental neurotoxicity studies. Additionally, this dose would be protective of the thyroid toxicity seen via the oral route in multiple species after various exposure durations (90-day, 1-year and 2-years). Because the PODs are similar for both the subchronic and chronic studies, there are no concerns that the effects will worsen following longer treatment. The 10X inter-species safety factor for extrapolation from animal to human and 10X intra-species safety factor are both applied; the FQPA SF is reduced to 1X; the incidental oral LOC is therefore 100X.

No adverse effects were observed in the route-specific dermal toxicity study; however, since increased susceptibility was observed in the database, an oral point of departure was selected for dermal risk assessment because the dermal toxicity study did not evaluate developmental or reproductive endpoints. The 10X inter-species safety factor for extrapolation from animal to human and 10X intra-species safety factor are both applied; the FQPA SF (residential exposures only) is reduced to 1X; the dermal LOC is therefore 100X.

For inhalation endpoints, a route specific 28-day inhalation study is available. This study was previously recommended to be required (K. Rury., TXR 0056585, 03/07/2013) and was submitted and reviewed (V. Chen, TXR 0057749, 06/22/2018) and summarized in Section A.3. While this study did not show any adverse portal of entry or systemic effects at the highest concentration tested and thus may not be appropriate for endpoint selection, the animal equivalent dose (AED) for the NOAEL in this study is ≥118 mg/kg/day. This AED is at least 5X the oral POD of 22 mg/kg/day used for risk assessment, suggesting that the oral POD is adequately protective of inhalation exposures. In addition, the POD of 22 mg/kg/day is protective of the susceptibility seen in the data, and the 10X UF_{DB} and FQPA SF were removed.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Since, for this chemical, all endpoints and PODs are derived from the same toxicological effects, exposures from oral, dermal and inhalation exposure routes can be aggregated.

4.5.2 Cancer Classification and Risk Assessment Recommendation

The Cancer Assessment Review Committee (CARC) classified boscalid as "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", and, therefore, the quantification of human cancer risk is not recommended (J. Kidwell, TXR 0051289, 11/14/2002). The classification was based on data which were combined from two 2-year rat studies where males had a significant increasing trend and significant differences in pair-wise comparison with the controls for thyroid follicular cell adenomas. The increased incidence of these adenomas exceeded the historical control mean and range. This was supported by thyroid hypertrophy and hyperplasia of follicular cells, increased thyroid weights and mechanistic data. Combined study data for female rats showed only a borderline significant increasing trend for thyroid follicular cell adenomas. No increase over controls was noted in males or females for carcinomas. There was no increase in the incidence of any tumors of either sex in the 18-month mouse study. All mutagenic studies were negative with or without activation. Based on the overall weak evidence of carcinogenic effects, it is concluded that the RfD approach would be protective of both chronic toxicity and carcinogenic potential of this chemical.

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.3.1. Summary of Toxicological Doses and Endpoints for Boscalid for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations, including Infants and Children and Females 13-49 years of age)	NA; An appropriate endpoint attributable to a single dose was not identified. The abortions seen in the rabbit developmental study were occurred during late-term pregnancy after multiple exposures and are not considered to be an acute effect.			
Chronic Dietary (All Populations)	NOAEL= 22 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0.22 mg/kg/day cPAD = 0.22 mg/kg/day	Co-critical chronic rat and carcinogenicity rat studies LOAEL = 110 mg/kg/day based on thyroid lesions.
Incidental Oral Short-Term (1-30 days) & Intermediate-Term (1-6 months)	NOAEL= 22 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	Co-critical chronic rat and carcinogenicity rat studies LOAEL = 110 mg/kg/day based on thyroid lesions.
Dermal Short-Term (1-30 days) & Intermediate-Term (1-6 months)	NOAEL= 22 mg/kg/day *DAF=15%*	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	Co-critical chronic rat and carcinogenicity rat studies LOAEL = 110 mg/kg/day based on thyroid lesions.
Inhalation[a] Short-Term (1-30 days) & Intermediate-Term (1-6 months)	NOAEL= 22 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	Residential LOC for MOE = 100	Co-critical chronic rat and carcinogenicity rat studies LOAEL = 110 mg/kg/day based on thyroid lesions.
Cancer (oral, dermal, inhalation)	Classification: "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"; quantification of human cancer risk is not recommended.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. DAF = Dermal Absorption Factor. N/A = not applicable. a = Inhalation toxicity assumed to be equivalent to oral toxicity.

Table 4.5.3.2. Summary of Toxicological Doses and Endpoints for Boscalid for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 22 mg/kg/day *DAF=15%*	UF_A = 10x UF_H =10x	Occupational LOC for MOE = 100	Co-critical chronic rat and carcinogenicity rat studies LOAEL = 110 mg/kg/day based on thyroid lesions.
Inhalation[a] Short-Term (1-30 days) and Intermediate-term (1-6 months)	NOAEL= 22 mg/kg/day	UF_A = 10x UF_H=10x	Occupational LOC for MOE = 100	Co-critical chronic rat and carcinogenicity rat studies LOAEL = 110 mg/kg/day based on thyroid lesions.
Cancer (oral, dermal, inhalation)	Classification: "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"; quantification of human cancer risk is not recommended.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. DAF = Dermal Absorption Factor. a = Inhalation toxicity assumed to be equivalent to oral toxicity.

4.6 Endocrine Disruptor Screening Program

As required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for boscalid, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), boscalid is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." he EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a

chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[3] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

Plant commodities: The nature of boscalid residues in primary crops is adequately understood, based upon acceptable grape, lettuce, and bean metabolism studies. No significant metabolism of boscalid occurred in grapes or lettuce; unchanged parent was the only component identified, accounting for 92-98% and 99% total radioactive residues (TRR), respectively. In bean plants, boscalid metabolized slowly; unchanged parent was the major component identified, accounting for up to 72% TRR in dry bean seeds, and 99% TRR in bean plants.

HED has concluded that the parent compound, boscalid, is the sole residue of concern in primary crops for purposes of risk assessment and the tolerance expression.

Livestock Commodities: The nature of boscalid residues in livestock are adequately understood, based upon acceptable metabolism studies conducted on lactating goats and laying hens. In both goats and hens, parent boscalid, M510F01 (hydroxy metabolite), and M510F 02 (M510F01 glucuronide) were identified as the major residues, each with ≥10% TRR. No amide bridge cleavage products were identified. Based on the structural similarity of boscalid and M510F 01, and the fact that the enzymatic hydrolysis step in the proposed enforcement method will release M510F 02 back to free M510F 01, HED concluded that the combined residues of parent boscalid, M510F 01 and M510F02 are the residues of concern in livestock matrices for purposes of risk assessment and the tolerance expression.

Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Boscalid	Boscalid
	Rotational Crop	Boscalid	Boscalid
Livestock	Ruminant	Boscalid, M510F01 & M510F02	Boscalid, M510F01 & M510F02
	Poultry		

[3] See https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.		
Matrix	**Residues Included in Risk Assessment**	**Residues Included in Tolerance Expression**
Drinking Water	Boscalid	

5.2 Food Residue Profile

The residue chemistry database is sufficient to support current registrations. The nature of the residues in plants, rotational crops, and livestock is adequately understood. An adequate analytical method is available for enforcing tolerances in plant and livestock commodities. Adequate storage stability data are available to support the storage durations and conditions of samples of the registered crops. Adequate crop field trial data have been submitted to support the registered uses. The existing tolerances on livestock commodities are adequate. Adequate field rotational crop studies are available supporting the existing tolerances for indirect residues of boscalid in rotational crops. These data support the 14-day plant-back interval currently specified for crops without boscalid uses.

Boscalid residues concentrate on almond hulls, apple wet pomace, canola oil, citrus dried pulp, raisins, peanut (meal and oil), and soybean hulls.

5.3 Water Residue Profile

The Ecological Fate and Effects Division (EFED) provided drinking water estimates in support of the human health dietary risk assessment for registration review (T. Harris, D452879, 07/31/2019,). The new ground water Estimated Drinking Water Concentration (EDWC) for ornamentals is lower (436 µg/L) than what was previously modeled. Therefore, the previously modeled drinking water estimates were used for this risk assessment since the existing exposure values are conservative.

The existing estimated chronic groundwater EDWC is 697 µg/L. The maximum Tier 1 estimated chronic surface water EDWC is 26.4 µg/L. These are based on turf use. The ground water value is higher than the surface water value and was therefore used in the assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources." The drinking water assessment considered all existing uses (K. White, D409880, 04/30/2013). The EFED models and their descriptions are available at http://www.epa.gov/oppefed1/models/water/. See Table 5.3.

Table 5.3. Tier I EDWCs based on Boscalid Use on Turf.[1,2]	
Source of Drinking Water	**Boscalid estimated drinking water concentrations (µg/L)**
	Turf
	Annual Average or Post Breakthrough Average
Surface water	26.4
Groundwater	**697**

[1] These are the highest EDWCs (bold) for the registered uses.
[2] Previously estimated annual average surface water concentrations for turf was 26.4 µg/L. Previously estimated groundwater concentrations were 697µg/L (K. White, D409880, 04/30/2013)

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Since no observed adverse effects could be attributed to a single dose, an acute endpoint was not established. Therefore, an acute dietary exposure assessment was not conducted.

An unrefined chronic dietary analysis was performed using tolerance level residues, empirical and default DEEM processing factors, and 100 PCT. Dietary risk estimates were determined considering exposures from food plus drinking water. Boscalid exposure from the existing uses result in estimated risks that are below the Agency's level of concern for food plus drinking water. The drinking water estimate conducted for registration review is lower than what was previously estimated and used on the previous assessments. Therefore, HED did not revise the dietary assessment, and considers the existing dietary exposure estimates protective (L. Bacon, D440500, 05/30/2019).

5.4.2 Percent Crop Treated Used in Dietary Assessment

One hundred percent crop treated was assumed for chronic dietary analyses.

5.4.3 Acute Dietary Risk Assessment

Since no observed effects could be attributed to a single dose, an acute endpoint was not established. Therefore, an acute dietary exposure assessment was not conducted.

5.4.4 Chronic & Cancer Dietary Risk Assessments

The exposure estimates for food plus drinking water are 20% of the cPAD for the U.S. population and 57% for all infants (<1 year old), the most highly exposed population subgroup, and therefore, are not of concern.

5.4.5 Cancer Dietary Risk Assessment

A cancer dietary assessment was not conducted since boscalid was classified by the Cancer Assessment Review Committee (CARC) as "suggestive evidence of carcinogenicity"; therefore, quantification of human cancer risk is not recommended.

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Boscalid.[1]			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**% cPAD**
General U.S. Population	0.04	0.044001	20
All Infants (< 1 year old)		0.091577	42
Children 1-2 years old		**0.126264**	**57**
Children 3-5 years old		0.091395	42
Children 6-12 years old		0.050281	23
Youth 13-19 years old		0.031209	14
Adults 20-49 years old		0.038846	18
Adults 50-99 years old		0.040446	19
Females 13-49 years old		0.039085	18

[1]The population subgroup with the highest estimated chronic dietary (food + drinking water) exposure and risk is indicated by bold text.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

The majority of registered boscalid product labels with residential use sites (e.g., garden and trees) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use personal protective equipment (PPE). Therefore for these products, HED has made the assumption that they are not for homeowner use and has not conducted a quantitative residential handler assessment for them. However there is a residential product (Bonide FT09, Reg No. 4-488, 5.622% active ingredient) that does not require the handler wear specific clothing (e.g., long sleeve shirt/long pants). Therefore, HED has made the assumption that this product is for homeowner use and conducted a quantitative residential handler assessment.

6.1 Residential Handler Exposure/Risk Estimates

HED uses the term “handlers” to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

Boscalid is currently registered for a number of residential use sites. There is a product (EPA Reg # 4-488) that is for use by residential handlers and have been assessed for handler exposures. Dermal and inhalation exposures were combined since the toxic effects observed from these routes of exposure are the same. Dermal and inhalation risks were not of concern (MOE > LOC of 100) for any of the scenarios assessed. The total MOEs ranged from 2,400 to 33,000

The quantitative exposure/risk assessment developed for residential handlers is based on the scenarios listed in Table 6.1.1.

Table 6.1.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Formulation	Exposure Scenario	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Dermal		Inhalation		Total MOE[7]
						Dose (mg/kg/day)[3]	MOE[4]	Dose (mg/kg/day)[5]	MOE[6]	
Mixer/Loader/Applicator										
Liquid concentrate	Manually-pressurized handwand around gardens/trees	0.0076 lb ai/gal	5 gallons	63	0.018	0.0045	4900	0.0000086	2,600,000	4900
	Hose-end Sprayer around gardens/trees		11 gallons	58	0.0014	0.0091	2400	0.0000015	15,000,000	2400
	Backpack around gardens/trees		5 gallons	130	0.14	0.0093	2400	0.000067	330,000	2400
	Sprinkler can around gardens/trees		5 gallons	58	0.0014	0.0041	5300	0.00000067	33,000,000	5300
	Manually-pressurized handwand around gardens/trees	0.0000051 1b ai/ft^2	1200 ft^2	63	0.018	0.00072	30,000	0.0000014	16,000,000	30,000
	Hose-end Sprayer around gardens/trees			58	0.0014	0.00067	33,000	0.00000011	210,000,000	33,000
	Backpack around gardens/trees			130	0.14	0.0015	15,000	0.000011	2,100,00	15,000
	Sprinkler can around gardens/trees			58	0.0014	0.00067	33,000	0.00000011	210,000,000	33,000

1 Based on residential registered label (Table B.2 Appendix B, EPA Reg # 4-488).
2 Based on HED's 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) × Dermal Absorption Factor (15%) ÷ Body Weight (80 kg).
4 Dermal MOE = Dermal POD (22 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (80 kg).
6 Inhalation MOE = Inhalation POD (22 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
7 Total MOE = POD (22 mg/kg/day) ÷ (Dermal Dose mg/kg/day + Inhalation Dose mg/kg/day)

6.2 Residential Post-application Exposure/Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with boscalid. The quantitative exposure/risk assessment for residential post-application exposures is based on the scenarios listed in Table 6.2.1.

Outdoor post-application dermal exposure has been assessed for applications to turf (golf course only) and gardens/trees. The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[4]. While not the only lifestage

[4] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

DFR Data: A total of four chemical-specific dislodgeable foliar residue (DFR) data sets have been submitted for boscalid for the following crops: (MRID 45405302, S. Tadayon, D454058, 09/09/2019) tomatoes, (MRID 45405303, S. Tadayon, D454059, 09/09/2019) grapes, (MRID 45405304, S. Tadayon, D454060, 09/09/2019) peaches, and (MRID 45405305, S. Tadayon, D454061, 09/09/2019) strawberry. All four studies have been reviewed by HED and were found to be acceptable for risk assessment. For the post-application residential scenarios, HED has used the peach and strawberry DFR data as it best represented the residential use profile for use on trees, garden ornamentals and garden fruits. A summary of these studies may be found in *Occupational and Residential Exposure Assessment for the Registration Review of Boscalid, (S.Tadayon, D453912, 08/01/2019)*.

TTR Data: A chemical-specific turf transferrable reside (TTR) study has been submitted and reviewed for boscalid (MRID 45405301, S. Tadayon, D454057, 09/09/2019) A summary of this study may be found in A summary of these studies may be found in *Occupational and Residential Exposure Assessment for the Registration Review of Boscalid, (S. Tadayon, D453912, 08/01/2019)*.

Residential Post-application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor are detailed in the 2012 Residential SOPs[4].

Application Rate: The registered application rates of boscalid on ornamentals and golf course turf are listed in Tables E.1 and E.2 in appendix E (includes occupational handler uses for residential sites).

Exposure Duration: Residential exposure is expected to be short-term in duration only.

Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[5].

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

None of the residential post-application exposures resulted in risk estimates of concern (all MOEs ≥ LOC of 100).

[5] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Boscalid.						
Lifestage	**Post-application Exposure Scenario**		**Application Rate[1]**	**DFR[2]/TTR[3] (μg/cm²)**	**Dose (mg/kg/day)[4]**	**MOEs (LOC = 100)[5]**
	Use Site	**Route of Exposure**				
Lawns and Turf						
Adult	Golfing	Dermal	0.35 lbs ai/A	0.389	0.0019	12,000
Child 6 to <11 years					0.0022	10,000
Child 11 to <16 years					0.0026	8,600
Garden and Trees						
Adult	Gardens	Dermal	0.70 lb ai/A	1.945	0.118	190
	Trees				0.053	410
Child 6 to <11 years	Gardens	Dermal	0.70 lb ai/A		0.081	270
	Trees				0.036	610

1 Based on registered labels
2 DFR = Based on a strawberry DFR study (MRID # 45405305) used for residential garden crops and a Peach DFR study (MRID# 45405304) used for residential tree crops.
3 TTR = Based on a TTR study (MRID# 45405301)
4 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
5 MOE = POD (22 mg/kg/day) ÷ Dose (mg/kg/day).

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for boscalid.

- The recommended residential exposure for use in the adult aggregate assessment is dermal exposure to gardens treated with liquid formulations;
- The recommended residential exposure for use in the youth 11 <16 years old aggregate assessment is dermal exposure from treated golf courses with liquid formulations;
- The recommended residential exposure for use in the children 6 to <11 years old aggregate assessment is dermal exposure to gardens with liquid formulations.

Table 6.3.1. Residential Risk Estimates for Use in Aggregate Assessment.						
Residential Post-application						
Scenario	**Dose (mg/kg/day)[2]**			**MOEs[3]**		
	Dermal	**Inhalation**	**Oral**	**Dermal**	**Inhalation**	**Oral**
Adult[1]	0.118	NA	NA	190	NA	NA
Youth (11 < 16 years)[1]	0.0026	NA	NA	8,600	NA	NA
Children (6 to <11 years)[1]	0.081	NA	NA	270	NA	NA

1 Adults -Post-application scenario = exposure to gardens/trees treated with liquid formulation
2 Residential Post-application Dose = the highest dose for each applicable lifestage of all scenarios assessed from Table 6.2.1.
3 Residential Post-application MOE = the MOEs associated with the highest doses identified in Table 6.2.1.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate

assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. For boscalid, the toxicological effect and uncertainty factors used for dietary (chronic), are the same as that for dermal (short- and intermediate-term) and inhalation (short-, and intermediate-term), and therefore exposures can be combined and used to estimate a total aggregate MOE.

7.1 Acute Aggregate Risk

The aggregate acute risk estimates include exposure to residues of boscalid in food and drinking water, and does not include dermal, inhalation, or incidental oral exposure. However, since no observed effects could be attributed to a single dose, an acute endpoint was not established. Therefore, an acute dietary exposure assessment was not conducted.

7.2 Short-Term Aggregate Risks

There is potential short-term exposure to boscalid via dietary (which is considered background exposure) and residential (which is considered primary) exposure pathways. These pathways lead to exposure via oral (background) as well as dermal and inhalation (primary) routes. The most conservative scenarios were chosen for each. For a description of the residential exposure scenarios considered in the aggregate assessment, see Section 6.1.

The short-term aggregate MOEs are 170 for children 6 to 11 years old, 650 for youth 11 to 16 years old, and 140 for adults. None of these aggregate risk estimates are of concern to HED.

Table 7.2. Short-Term and/or Intermediate Term Aggregate Risk Calculations.

Population	Short- or Intermediate-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day [4]	Aggregate MOE (food, water, and residential)[5]
Adults[6]	21.8	100	0.218	0.040446[7]	0.118	0.158446	140
Youth 11-16				0.031209[8]	0.0026	0.033809	650
Children 6-11				0.050281[9]	0.081	0.131281	170

[1] 10x for inter- and 10x intra- species uncertainty factors, totaling 100.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Residential Exposure = Dermal exposure only. Refer to Table 6.1 for further information.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure).
[5] Aggregate MOE = [NOAEL/(Avg Food & Water Exposure + Residential Exposure)].
[6] The highest exposure for adults results from post-application dermal exposures. The highest combined dermal + inhalation residential handler exposure is 0.009367, resulting from mixing/loading/applying liquid formulations to gardens/trees via backpack sprayer.
[7] Dietary exposure subpopulation for adults represented by Adults 50-99.
[8] Dietary exposure subpopulation for youth 11-16 represented by youth 13-19.
[9] Dietary exposure subpopulation for children 6-11 represented by children 6-12.

7.3 Chronic Aggregate Risk

Chronic exposure from the residential pathway is not anticipated based on the current boscalid use pattern. The chronic aggregate risk (food and drinking water) is below HED's LOC (i.e., <100% cPAD for the general U.S. population and all population subgroups). See Section 5.4.6 for details.

8.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2014-0219-0003&disposition=attachment&contentType=pdf). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for boscalid.

9.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for boscalid. The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information). [6] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children

[6] Available: http://www.epa.gov/reducing-pesticide-drift

playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[7] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of boscalid**.** In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[8] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). The screening level drift related risk estimates are presented below. In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

[7] This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.
[8] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift

9.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Boscalid is used on a variety of crops and can be applied via airblast, aerial and groundboom equipment at a maximum application rate of 0.7 lb ai/A for all referenced equipments. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.

- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).

- **Orchard airblast applications** are based on the AgDrift option for Sparse (Young/Dormant) tree canopies.

In addition to the screening level spray drift scenarios described above, additional results are provided which represent viable drift reduction technologies (DRTs) that represent potential risk management options (S. Tadayon, D453912, 08/01/2019). In particular, different spray qualities have been considered as well as the impact of other application conditions (e.g., boom height, use of a helicopter instead of fixed wing aircraft, crop canopy conditions).

For adults, the screening level scenario indicates that the dermal MOEs are acceptable (MOEs ≥ 100) at the edge of the field. Dermal and incidental oral risk estimates for children 1 to <2 years old were combined because the toxicity endpoint for each route of exposure is based on the same toxicological effect. For children 1 to <2 years old, combined dermal and incidental oral risk estimate indicates the MOEs ≥ 100 and are acceptable at the edge of the field.
Furthermore, spray drift risk estimates were refined by using chemical-specific turf transferable residue (TTR) data submitted for boscalid (MRID 45405301). The study has been reviewed by HED and was found to be acceptable for risk assessment (S. Tadayon, D454057, 09/09/2019). The predicted DAT-0 residue value of 0.047 µg/cm^2 from the Pennsylvania site was used in the assessment, adjusted for differences in application rates between study and label. Adjusted TTR value of 0.094 µg/cm^2 was used to estimate risks. Results are presented in Tables 9.1.1 and 9.1.2 and indicate no risks of concern.

Table 9.1.1 Adult Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Boscalid - Dermal Route of Exposure

Application Equipment	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	TTR[a] (ug/cm^2)	Dermal Dose (mg/kg/day)	At Edge Dermal MOE[b] (LOC=100)
Aerial	***Fine to Medium***	0.7	0.094	0.0123	1,800
Groundboom	***High Boom Very fine to Fine***			0.0089	2,500
Airblast	***Sparse***			0.0068	3,200

a. TTR (0.047 ug/cm^2) on day zero from TTR study with MRID# 45405301. Study application rate was 0.349 lb ai/A
b. MOEs at various distances from field edge = dermal (22 mg/kg/day) ÷ Dose (mg/kg/day), where the dermal dose is calculated using the algorithms provided in the Turf Residential SOPs (http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide), and the TTR used in the calculations is the estimated TTR * drift fraction of spray drift that deposits on lawns at various distances from the field edge

Table 9.1.2 Children (1<2 years old) Risk Estimates (Combined MOE) Related to Indirect Exposure to Spray Drift for Boscalid - Combined Dermal and Oral Routes of Exposure

Application Equipment	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	TTR (ug/cm^2)	At Edge Dermal MOE (LOC 100)	At Edge HtM MOE (LOC 100)	At Edge Total MOE[b] (LOC 100)
Aerial	***Fine to Medium***	0.7	0.094	910	6,600	800
Groundboom	***High Boom Very fine to Fine***			1,200	9,100	1,100
Airblast	***Sparse***			1,600	12,000	1,400

a. TTR (0.047 ug/cm^2) on day zero from TTR study with MRID# 45405301. Study application rate was 0.349 lb ai/A
b. Total MOE = Total MOE = 1 ÷ (1/Dermal MOE + 1/Incidental Oral MOE).

Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to boscalid and any other substances and boscalid does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that boscalid has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[9] and conducting cumulative risk assessments (CRA)[10]. During Registration Review, the agency will utilize this framework to determine if the available toxicological data for boscalid suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

10.0 Occupational Exposure/Risk Characterization

11.0 Short-/Intermediate-Term Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being

[9] *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)
[10] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the registered use patterns and current labeling, types of equipment and techniques that can potentially be used, short- and intermediate-term occupational handler exposure is expected from the registered uses. The occupational handler exposure data and assumptions are available in the occupational and residential exposure assessment for this action (S. Tadayon, D453912, 08/01/2019).

Combining Exposures/Risk Estimates:
Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined dermal + inhalation dose (mg/kg/day)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
The majority of the occupational handler dermal, inhalation and combined (dermal plus inhalation) exposures did not result in risk estimates of concern (MOEs ≥ 100) with baseline attire. Only one scenario (mixer/loader of dry flowable (DF) formulation for aerial application to high-acreage field crops) resulted in MOEs less than the LOC at baseline attire (Dermal MOE = 89; Total (dermal plus inhalation) MOE = 71). This scenario is not of concern with the addition of gloves (Dermal MOE = 390; Total (dermal plus inhalation) MOE = 180). The majority of occupational labels require baseline personal protective equipment (PPE), consisting of single layer clothing (long sleeve shirt, long pants, socks and shoes), and chemical resistant gloves. Some labels also require the use of additional PPE such as double layer clothing, protective eye wear and NIOSH filtering half-face respirators. A summary of the occupational handler exposure and risk estimates resulting from agricultural uses and seed treatment are provided in Tables 11.1. and 11.2 respectively.

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated [2]**	**Unit Exposures [3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose [4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
Mixer/Loader										
Mixing/Loading DF formulations for Aerial Application	Nursery (ornamentals, vegetables, trees, container stock)	0.70 lb ai/acre	60 acres	227	8.96	0.0179	1,200	0.0047	4,700	960
	Orchard/Vineyard	0.362 lb ai/acre	350 acres	227	8.96	0.054	410	0.0143	1,500	320
	Field crop, typical	0.547 lb ai/acre	350 acres	227	8.96	0.0816	270	0.0215	1,000	210
	Field crop, high-acreage	0.481 lb ai/acre	1200 acres	227	8.96	0.246	**89**	0.0646	340	**71**
				51.6 (SL/G)		0.0559	390			180
Mixing/Loading DF formulations for Dip Treatment of Ornamentals	Animal (direct), livestock as a surrogate for Dip Treatment of Ornamentals	0.007 lb ai/gallon	100 gallons	227	8.96	0.000298	74,000	0.0000784	280,000	59,000
Mixing/Loading DF formulations for Airblast Application	Nursery (ornamentals, vegetables, trees, container stock)	0.70 lb ai/acre	20 acres	227	8.96	0.00596	3700	0.00156	14,000	2,900
	Orchard/Vineyard	0.441 lb ai/acre	40 acres	227	8.96	0.0075	2900	0.00198	11,000	2,300
Mixing/Loading DF formulations for Chemigation Application	Orchard/Vineyard	0.441 lb ai/acre	350 acres	227	8.96	0.0656	340	0.0173	1,300	270
	Field crop, typical	0.547 lb ai/acre	350 acres	227	8.96	0.0816	270	0.0215	,1000	210
	Field crop, high-acreage	0.481 lb ai/acre	350 acres	227	8.96	0.0716	310	0.0189	1,200	250
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.70 lb ai/acre	60 acres	227	8.96	0.0179	1200	0.0047	4,700	960
	Nursery (ornamentals,	0.70 lb ai/acre	60 acres	227	8.96	0.0179	1200	0.0047	4,700	960

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated[2]**	**Unit Exposures[3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
	vegetables, trees, container stock)									
Mixing/Loading DF formulations for Groundboom Application	Golf course (tees and greens only)	0.35 lb ai/acre	5 acres	227	8.96	0.000744	30,000	0.000196	110,000	24,000
	Golf course (fairways, tees, greens)	0.35 lb ai/acre	40 acres	227	8.96	0.00596	3,700	0.00156	14,000	2,900
	Field-grown ornamental crops	0.70 lb ai/acre	40 acres	227	8.96	0.0119	1,800	0.00314	7,000	1,400
	Nursery (ornamentals, vegetables, trees, container stock)	0.70 lb ai/acre	60 acres	227	8.96	0.0179	1,200	0.0047	4,700	960
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.70 lb ai/acre	60 acres	227	8.96	0.0179	1,200	0.0047	4,700	960
	Orchard/Vineyard	0.441 lb ai/acre	40 acres	227	8.96	0.0075	2,900	0.00198	11,000	2,300
	Field crop, typical	0.547 lb ai/acre	80 acres	227	8.96	0.0186	1,200	0.0049	4,500	950
	Field crop, high-acreage	0.481 lb ai/acre	200 acres	227	8.96	0.0409	540	0.0108	2,000	430
Mixing/Loading Liquids for Groundboom Application	Field-grown ornamental crops	0.326 lb ai/acre	40 acres	220	0.219	0.00538	4,100	0.0000358	610,000	4,100
	Nursery (ornamentals, vegetables, trees, container stock)	0.326 lb ai/acre	60 acres	220	0.219	0.00806	2,700	0.0000535	410,000	2,700
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.326 lb ai/acre	60 acres	220	0.219	0.00806	2,700	0.0000535	410,000	2,700

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated [2]**	**Unit Exposures [3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose [4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
Applicator										
Applying Sprays with Aerial Application Equipment	Nursery (ornamentals, vegetables, trees, container stock)	0.70 lb ai/acre	60 acres	2.08 (EC)	0.0049 (EC)	0.000164	130,000	0.00000258	8,500,000	130,000
	Orchard/Vineyard	0.362 lb ai/acre	350 acres	2.08 (EC)	0.0049 (EC)	0.000495	44,000	0.00000776	2,800,000	43,000
	Field crop, typical	0.547 lb ai/acre	350 acres	2.08 (EC)	0.0049 (EC)	0.000746	29,000	0.0000117	1,900,000	29,000
	Field crop, high-acreage	0.481 lb ai/acre	1200 acres	2.08 (EC)	0.0049 (EC)	0.00225	9,800	0.0000354	620,000	9,600
Applying Sprays with Airblast Application Equipment	Nursery (ornamentals, vegetables, trees, container stock)	0.70 lb ai/acre	20 acres	1770	4.71	0.0465	470	0.000824	27,000	460
	Orchard/Vineyard	0.441 lb ai/acre	40 acres	1770	4.71	0.0585	380	0.00104	21,000	370
Applying Sprays with Groundboom Application Equipment	Golf course (tees and greens only)	0.35 lb ai/acr	5 acres	78.6	0.34	0.000259	85,000	0.00000744	3,000,000	83,000
	Golf course (fairways, tees, greens)	0.35 lb ai/acre	40 acres	78.6	0.34	0.00206	11,000	0.0000595	370,000	11,000
	Field-grown ornamental crops	0.70 lb ai/acre	40 acres	78.6	0.34	0.00413	5,300	0.000119	180,000	5,100
	Nursery (ornamentals, vegetables, trees, container stock)	0.70 lb ai/acre	60 acres	78.6	0.34	0.00619	3,600	0.000179	120,000	3,500
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.70 lb ai/acre	60 acres	78.6	0.34	0.00619	3,600	0.000179	120,000	3,500
	Orchard/Vineyard	0.441 lb ai/acre	40 acres	78.6	0.34	0.00261	8,400	0.000075	290,000	8,200
	Field crop, typical	0.547 lb ai/acre	80 acres	78.6	0.34	0.00645	3,400	0.000186	120,000	3,300

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated [2]**	**Unit Exposures [3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose [4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
	Field crop, high-acreage	0.481 lb ai/acre	200 acres	78.6	0.34	0.0142	1,500	0.000409	54,000	1,500
Applying Liquid Formulation - Dip (manual)	Animal (direct), livestock as a surrogate for Dip Treatment of Ornamentals	0.007 lb ai/gallon	100 gallons	54300	26.6	0.0713	310	0.000233	94,000	310
Flagger										
Flagging for Aerial Applications (Sprays)	Nursery (ornamentals, vegetables, trees, container stock)	0.70 lb ai/acre	60 acres	11	0.35	0.000866	25,000	0.000184	120,000	21,000
	Orchard/Vineyard	0.362 lb ai/acre	350 acres	11	0.35	0.00261	8,400	0.000554	40,000	6,900
	Field crop, typical	0.547 lb ai/acre	350 acres	11	0.35	0.00396	5,600	0.000838	26,000	4,600
	Field crop, high-acreage	0.481 lb ai/acre	350 acres	11	0.35	0.00347	6,300	0.000736	30,000	5,200
Mixer/Loader/Applicator										
Mixing/Loading/Applying DF formulations with a Backpack	Orchard/Vineyard	0.00221 lb ai/gallon	40 gallons	8260	2.58	0.00137	16,000	0.00000285	7,700,000	16,000
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.007 lb ai/gallon	40 gallons	13200	140	0.00694	3,200	0.00049	45,000	3,000
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon	40 gallons	58400	69.1	0.0308	710	0.000241	91,000	700
	Nursery (ornamentals, vegetables, trees, container stock) - Ground/soil-directed	0.007 lb ai/gallon	40 gallons	8260	2.58	0.00433	5,100	0.00000903	2,400,000	5,100

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated[2]**	**Unit Exposures[3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
	Landscaping, trees/shrubs/bushes	0.007 lb ai/gallon	40 gallons	58,400	69.1	0.0308	710	0.000241	91,000	700
	Landscaping, plants/flowers	0.007 lb ai/gallon	40 gallons	58,400	69.1	0.0308	710	0.000241	91,000	700
Mixing/Loading/Applying DF formulations with a Manually-pressurized Handwand	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.007 lb ai/gallon	40 gallons	100,000	30	0.0525	420	0.000105	210,000	420
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon	40 gallons	100,000	30	0.0525	420	0.000105	210,000	420
	Landscaping, trees/shrubs/bushes	0.007 lb ai/gallon	40 gallons	100,000	30	0.0525	420	0.000105	210,000	420
	Landscaping, plants/flowers	0.007 lb ai/gallon	40 gallons	100,000	30	0.0525	420	0.000105	210,000	420
Mixing/Loading/Applying DF formulations with a Mechanically-pressurized Handgun	Orchard/Vineyard	0.00221 lb ai/gallon	1000 gallons	6050	8.68	0.0251	880	0.00024	92,000	870
	Orchard/Vineyard - Drench/Soil-/Ground-directed	0.00221 lb ai/gallon	1000 gallons	6050	8.68	0.0251	880	0.00024	92,000	870
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.007 lb ai/gallon	1000 gallons	3500	120	0.0459	480	0.0105	2,100	390
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables) - Drench/Soil-/Ground-directed	0.007 lb ai/gallon	1000 gallons	3500	120	0.0459	480	0.0105	2,100	390

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated[2]**	**Unit Exposures[3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
	Golf course (tees and greens only)	0.35 lb ai/acre	5 acres	1960	42	0.00643	3,400	0.000919	24,000	3,000
	Golf course (fairways, tees, greens)	0.35 lb ai/acre	5 acres	1960	42	0.00643	3,400	0.000919	24,000	3,000
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon	1000 gallons	6050	8.68	0.0795	280	0.00076	29,000	280
	Nursery (ornamentals, vegetables, trees, container stock) - Drench/Soil-/Ground-directed	0.007 lb ai/gallon	1000 gallons	6050	8.68	0.0795	280	0.00076	29,000	280
	Landscaping, trees/shrubs/bushes	0.007 lb ai/gallon	1000 gallons	6050	8.68	0.0795	280	0.00076	29,000	280
	Field crop, typical	0.00547	1000 gallons	6050	8.68	0.0621	350	0.000594	37,000	350
	Field crop, typical - Drench/Soil-/Ground-directed	0.00547 lb ai/gallon	1000 gallons	6050	8.68	0.0621	350	0.000594	37,000	350
Mixing/Loading/Applying Liquid formulations with a Backpack	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.00326 lb ai/gallon	40 gallons	13,200	140	0.00323	6,800	0.000229	96,000	6,400
	Nursery (ornamentals, vegetables, trees, container stock)	0.00326 lb ai/gallon	40 gallons	58,400	69.1	0.0143	1,500	0.000113	190,000	1,500
	Nursery (ornamentals, vegetables, trees, container stock) -	0.00326 lb ai/gallon	40 gallons	8260	2.58	0.00203	11,000	0.0000042	5,200,000	11,000

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated [2]**	**Unit Exposures [3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose [4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
	Ground/soil-directed									
	Landscaping, trees/shrubs/bushes	0.00326 lb ai/gallon	40 gallons	58,400	69.1	0.0143	1,500	0.000113	190,000	1,500
	Landscaping, plants/flowers	0.00326 lb ai/gallon	40 gallons	58,400	69.1	0.0143	1,500	0.000113	190,000	1,500
Mixing/Loading/Applying Liquid formulations with a Manually-pressurized Handwand	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.00326 lb ai/gallon	40 gallons	100,000	30	0.0244	900	0.0000489	450,000	900
	Nursery (ornamentals, vegetables, trees, container stock)	0.00326 lb ai/gallon	40 gallons	100,000	30	0.0244	900	0.0000489	450,000	900
	Landscaping, trees/shrubs/bushes	0.00326 lb ai/gallon	40 gallons	100,000	30	0.0244	900	0.0000489	450,000	900
	Landscaping, plants/flowers	0.00326 lb ai/gallon	40 gallons	100,000	30	0.0244	900	0.0000489	450,000	900
Mixing/Loading/Applying Liquid formulations with a Mechanically-pressurized Handgun	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.00326 lb ai/gallon	1000 gallons	3500	120	0.0214	1,000	0.00489	4,500	820
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.00326 lb ai/gallon	1000 gallons	3500	120	0.0214	1,000	0.00489	4,500	820
	Nursery (ornamentals, vegetables, trees, container stock)	0.00326 lb ai/gallon	1000 gallons	6050	8.68	0.0369	600	0.000354	62,000	590
	Nursery (ornamentals,	0.00326 lb ai/gallon	1000 gallons	6050	8.68	0.0369	600	0.000354	62,000	590

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Boscalid.										
Exposure Scenario	**Crop / Target Category**	**Maximum Application Rate[1]**	**Amount Handled / Area Treated[2]**	**Unit Exposures[3] (ug/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total MOE (LOC = 100)[6]**
				Dermal	**Inhalation**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	**Dose[4] (mg/kg-day)**	**MOE (LOC = 100)[5]**	
	vegetables, trees, container stock)									
	Landscaping, trees/shrubs/bushes	0.00326 lb ai/gallon	1000 gallons	6050	8.68	0.0369	600	0.000354	62,000	590

1 Assessment based on maximum registered application rate for each scenario. Crops were grouped according to application rates and applicable exposure scenarios to cover all uses.
2 Based on ExpoSAC Policy 9.1.
3 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data). Level of mitigation: Baseline unless shown otherwise.
4 Dose = Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/ gal or lb ai/A) × Area Treated or Amount Handled Daily (gal/day or A/day) x DAF (15%) ÷ BW (80 kg).
5 MOE = POD (22 mg/kg/day) ÷ Dose (mg/kg/day). Bold MOEs represent estimates of concern (LOC = 100).
6 Total MOE = POD (22 mg/kg/day) ÷ (Dermal Dose mg/kg/day + Inhalation Dose mg/kg/day)

Table 11.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Commercial Seed Treatment Uses of Boscalid.										
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[1] lb ai/lb seed**	**Amount Handled Daily[2] lbs/day**	**Unit Exposures[3] (µg/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total**
				Dermal	**Inhalation**	**Dose[4] (mg/kg/day)**	**MOE (LOC = 100)[5]**	**Dose[6] (mg/kg/day)**	**MOE (LOC = 100)[7]**	**MOE (LOC = 100)[8]**
Seed Treatment										
Loader/Applicator	*Brassica* (Head and Stem) Vegetables	0.000809	3000	23 (SL/G)	0.34 (No-R)	0.000105	210,000	0.0000103	2,100,000	190,000
	Bulb Vegetables	0.000809	3000			0.000105	210,000	0.0000103	2,100,000	190,000
	Canola\Rape	0.000809	125,000			0.00437	5000	0.00043	51,000	4,600
	Cotton	0.000809	125,000			0.00437	5000	0.00043	51,000	4,600
	Cucurbit Vegetables	0.000809	3000			0.000105	210,000	0.0000103	2,100,000	190,000
	Legume Vegetables	0.000404	339,500			0.00591	3700	0.000583	38,000	3,400
	Roquette (Arugula)	0.000809	3000			0.000105	210,000	0.0000103	2,100,000	190,000
	Soybeans	0.000404	281,250			0.00489	4500	0.000483	46,000	4,100
	Sunflower	0.000404	80,000			0.00139	16,000	0.000138	160,000	15,000
Sewer	*Brassica* (Head and Stem) Vegetables	0.000809	3000	6.2 (No-G)	0.23 (No-R)	0.0000281	780,000	0.00000698	3,200,000	630,000
	Bulb Vegetables	0.000809	3000			0.0000281	780,000	0.00000698	3,200,000	630,000
	Canola\Rape	0.000809	125,000			0.00118	19,000	0.000291	76,000	15,000

Table 11.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Commercial Seed Treatment Uses of Boscalid.										
Exposure Scenario	**Crop or Target**	**Maximum Application Rate[1] lb ai/lb seed**	**Amount Handled Daily[2] lbs/day**	**Unit Exposures[3] (µg/lb ai) Baseline or (PPE)**		**Dermal**		**Inhalation**		**Total**
				Dermal	**Inhalation**	**Dose[4] (mg/kg/day)**	**MOE (LOC = 100)[5]**	**Dose[6] (mg/kg/day)**	**MOE (LOC = 100)[7]**	**MOE (LOC = 100)[8]**
	Cotton	0.000809	125,000			0.00118	19,000	0.000291	76,000	15,000
	Cucurbit Vegetables	0.000809	3000			0.0000281	780,000	0.00000698	3,200,000	630,000
	Legume Vegetables	0.000404	339,500			0.00159	14,000	0.000394	56,000	11,000
	Roquette (Arugula)	0.000809	3000			0.0000281	780,000	0.00000698	3,200,000	630,000
	Soybeans	0.000404	281,250			0.00132	17,000	0.000326	67,000	14,000
	Sunflower	0.000404	80,000			0.000375	59,000	0.0000929	240,000	47,000
Bagger	*Brassica* (Head and Stem) Vegetables	0.000809	3000	9.1 (No-G)	0.16 (No-R)	0.0000414	530,000	0.00000485	4,500,000	470,000
	Bulb Vegetables	0.000809	3000			0.0000414	530,000	0.00000485	4,500,000	470,000
	Canola\Rape	0.000809	125,000			0.00173	13,000	0.000203	110,000	12,000
	Cotton	0.000809	125,000			0.00173	13,000	0.000203	110,000	12,000
	Cucurbit Vegetables	0.000809	3000			0.0000414	530,000	0.00000485	4,500,000	470,000
	Legume Vegetables	0.000404	339,500			0.00234	9400	0.000274	80,000	8400
	Roquette (Arugula)	0.000809	3000			0.0000414	530,000	0.00000485	4,500,000	470,000
	Soybeans	0.000404	281,250			0.00193	11,000	0.000228	96,000	9,900
	Sunflower	0.000404	80,000			0.000551	40,000	0.0000646	340,000	36,000
Multiple Activities	*Brassica* (Head and Stem) Vegetables	0.000809	3000	42 (SL/G)	1.6 (No-R)	0.000191	120,000	0.0000485	450,000	95,000
	Bulb Vegetables	0.000809	3000			0.000191	120,000	0.0000485	450,000	95,000
	Canola\Rape	0.000809	125,000			0.00797	2800	0.00203	11,000	2,200
	Cotton	0.000809	125,000			0.00797	2800	0.00203	11,000	2,200
	Cucurbit Vegetables	0.000809	3000			0.000191	120,000	0.0000485	450,000	95,000
	Legume Vegetables	0.000404	339,500			0.0108	2000	0.00274	8000	1,600
	Roquette (Arugula)	0.000809	3000			0.000191	120,000	0.0000485	450,000	95,000
	Soybeans	0.000404	281,250			0.00894	2500	0.00228	9600	2,000
	Sunflower	0.000404	80,000			0.00255	8600	0.000646	34000	6,900
Planters	*Brassica* (Head and Stem) Vegetables	0.000809	211	250 (SL/G)	3.4 (No-R)	0.0000801	270,000	0.00000725	3,000,000	250,000
	Bulb Vegetables	0.000809	2000			0.000759	29,000	0.0000688	320,000	27,000
	Canola\Rape	0.000809	1650			0.000626	35,000	0.0000568	390,000	32,000
	Cotton	0.000809	3780			0.00143	15,000	0.00013	170,000	14,000
	Cucurbit Vegetables	0.000809	929			0.000353	62,000	0.000032	690,000	57,000
	Legume Vegetables	0.000404	46,100			0.00874	2500	0.000791	28,000	2,300

Table 11.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Commercial Seed Treatment Uses of Boscalid.										
Exposure Scenario	Crop or Target	Maximum Application Rate[1] lb ai/lb seed	Amount Handled Daily[2] lbs/day	Unit Exposures[3] (µg/lb ai) Baseline or (PPE)		Dermal		Inhalation		Total
				Dermal	Inhalation	Dose[4] (mg/kg/day)	MOE (LOC = 100)[5]	Dose[6] (mg/kg/day)	MOE (LOC = 100)[7]	MOE (LOC = 100)[8]
	Roquette (Arugula)	0.000809	2000			0.000759	29,000	0.0000688	320,000	27,000
	Soybeans	0.000404	33,300			0.0063	3500	0.000571	39,000	3,200
	Sunflower	0.000404	320			0.0000606	360,000	0.0000055	4,000,000	330,000

1 Based on registered labels
2 Based on HED ExpoSAC Policy 15.2 and the BEAD memo: "Acres Planted per Day and Seeding Rates of Crops Grown in the United States;" Level of mitigation: Baseline (SL- no-G), SL/G = Single layer/Gloves and No-R = no respirator.
3 ExpoSAC Policy 14: SOPs for Seed Treatment (May 1, 2003).
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) × DAF (15%) ÷ BW (80 kg).
5 Dermal MOE = Dermal POD (22 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation POD (22 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8. Total MOE = POD (22 mg/kg/day) ÷ (Dermal Dose mg/kg/day + Inhalation Dose mg/kg/day)

11.1 Occupational Post-Application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.2.1 Occupational Post-Application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for boscalid.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios. Additionally, the Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements. [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)]

11.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

Occupational Post-application Dermal Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, short- and intermediate-term

occupational post-application dermal exposure is expected from the registered uses. The occupational exposure data and assumptions are available in the occupational and residential exposure assessment for this action (S. Tadayon, D453912, 08/01/2019).

Dislodgeable Foliar Residues:
DFR Data: A total of four chemical-specific DFR data sets have been submitted for boscalid for the following crops: (MRID 45405302, S. Tadayon, D454058, 09/09/2019) tomatoes, (MRID 45405303, S. Tadayon, D454059, 09/09/2019) grapes, (MRID 45405304, S. Tadayon, D454060, 09/09/2019) peaches, and (MRID 45405305, S. Tadayon, D454061, 09/09/2019) strawberry. All four studies have been reviewed by HED and were found to be acceptable for risk assessment. For the post-application occupational scenarios, HED has used the peach DFR data for all orchard crops, grape DFR data for vine and trellis crops, tomato DFR data for berry, low, field / row crop, low / medium, field / row crop, tall, nursery crop (ornamentals, non-bearing plants), greenhouse crop (ornamentals, non-bearing plants), vegetable, cucurbit, vegetable, fruiting, vegetable, head and stem *brassica*, vegetable, leafy and vegetable, stem / stalk and strawberry DFR data for strawberry. The California grape DFR data (MRID 454053-05) was used in this assessment. While HED understands that not all table grapes are grown in California, the DFR data from the other grape sites (DFR trial in PA and DFR trial in WA) was of lower quality than the boscalid DFR trial in CA.

Turf Transferable Residue (TTR): A chemical-specific TTR study has been submitted for boscalid (MRID 45405301, S. Tadayon, D454057, 09/09/2019). This study was used for golf course maintenance assessment.

Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in Appendix A.

Occupational Post-application Non-Cancer Dermal Risk Estimates
Although all post-application scenarios were quantitatively calculated, only the worst case scenarios and respective transfer coefficients are summarized in Table 8.2.2. Most of the dermal post-application exposure scenarios resulted in MOEs greater than the LOC (MOE ≥ 100) and are not of concern on Day 0. Risk estimates were of concern (MOE < 100) for girdling and turning grapes up to 22 days after applications at 0.362 lb ai/A.

Table 11.2.2. Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimates for Boscalid.

Policy Crop Group Category	Crops	Application Rate[1] (lb ai/A)	Maximum Transfer Coefficient[2] (cm^2/hr)	Activities for Maximum TC	DAT (Day After Treatment)	DFR[5,6,7,8]/TTR[9] Residue (ug/cm^2)	Dose[3] (mg/kg-day)	MOE (LOC = 100)[4]
Berry, low[5]	Bushberry	0.362	1900	Irrigation (hand set)	0	0.69	0.011	1,900
	Strawberry[8]	0.362	1100	Hand harvesting	0	1.76	0.029	760
Bunch/bundle[6]	Hop	0.441	1900	Irrigation (hand set)	0	0.96	0.027	800

Table 11.2.2. Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimates for Boscalid.

Policy Crop Group Category	Crops	Application Rate[1] (lb ai/A)	Maximum Transfer Coefficient[2] (cm^2/hr)	Activities for Maximum TC	DAT (Day After Treatment)	DFR[5,6,7,8]/TTR[9] Residue (ug/cm^2)	Dose[3] (mg/kg-day)	MOE (LOC = 100)[4]
	Tropical/sub-tropical fruit, inedible peel	0.291	1400	Harvesting, Hand	0	0.64	0.013	1,600
Field / row crop, low / medium[5]	Alfalfa; Bean, dry, and Pea, dry; Bean, snap	0.481	1900	Irrigation (hand set)	0	0.92	0.026	840
	Canola	0.263	1100	Scouting	0	0.50	0.008	2,700
	Cotton	0.394	5050	Harvesting, Mechanical, Tramper	0	0.79	0.060	370
	Herbs and spices (mint)	0.291	1900	Irrigation (hand set)	0	0.55	0.016	1,400
	Peanut	0.441	1900	Irrigation (hand set)	0	0.84	0.024	920
	Soybean	0.481	1100	Scouting	0	0.92	0.015	1,500
Field / row crop, tall[5]	Sunflower	0.394	90	Scouting	0	0.75	0.001	22,000
Tree, "fruit", deciduous[6]	Fruit, stone	0.228	3600	Thinning Fruit	0	0.64	0.027	820
	Fruit, pome	0.291	3600	Thinning Fruit	0	0.64	0.034	640
	Tropical/sub-tropical fruit, edible peel; tropical/sub-tropical fruit, inedible peel	0.291	1400	Harvesting, Hand	0	0.64	0.013	1,600
Tree, "fruit", evergreen[6]	Tropical/sub-tropical fruit, edible peel; tropical/sub-tropical fruit, inedible peel	0.291	3600	Thinning Fruit	0	0.64	0.034	640
	Fruit, citrus	0.291	1400	Hand harvesting	0			
Tree, "nut"[6]	Nuts	0.291	3600	Thinning Fruit	0	0.64	0.034	640
	Pistachio	0.228	1400	Harvesting, Hand	0	0.64	0.013	1,600
	Almond; Nut, tree	0.232	580	Scouting	0	0.64	0.006	4,000
Turf / sod[9]	Golf Course	0.35	3700	Maintenance	0	0.047	0.003	8,400
Unassigned[5]	Nursery Crop (Ornamentals, Non-bearing Plants)	0.70	1900	Irrigation (hand set)	0	1.33	0.038	580

Table 11.2.2. Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimates for Boscalid.

Policy Crop Group Category	Crops	Application Rate[1] (lb ai/A)	Maximum Transfer Coefficient[2] (cm^2/hr)	Activities for Maximum TC	DAT (Day After Treatment)	DFR[5,6,7,8]/TTR[9] Residue (ug/cm^2)	Dose[3] (mg/kg-day)	MOE (LOC = 100)[4]
	Greenhouse Crop (Ornamentals, Non-bearing Plants)	0.70	230	Harvesting, hand; Pruning, hand; Scouting; Container moving; Weeding, hand; Transplanting; Grafting; Propagating; Pruning, hand; Transplanting; Pinching, Tying/Training	0	1.33	0.005	4,800
Vegetable, "root"[5]	Carrot	0.341	1900	Irrigation (hand set)	0	0.65	0.019	1,200
	Potato	0.438	1900	Irrigation (hand set)	0	0.83	0.024	920
	Turnip	0.394	1900	Irrigation (hand set)	0	0.75	0.021	1,000
	Vegetable, bulb	0.298	4200	Weeding, Hand	0	0.57	0.036	610
	Vegetable, root and tuber	0.341	1900	Irrigation (hand set)	0	0.65	0.019	1,200
Vegetable, cucurbit[5]	Vegetable, cucurbit	0.291	1900	Irrigation (hand set)	0	0.55	0.016	1,400
Vegetable, fruiting[5]	Vegetable, fruiting	0.153	1900	Irrigation (hand set)	0	0.29	0.008	2,600
	Tomato	0.547	1900	Irrigation (hand set)	0	1.04	0.030	740
Vegetable, head and stem *Brassica*[5]	Head and Stem *Brassica*	0.394	4200	Scouting; Harvesting, Hand; Weeding, Hand; Topping; Hand-tying	0	0.75	0.047	4,700
Vegetable, leafy[5]	Head and Stem *Brassica*; Leafy *Brassica*	0.394	4200	Weeding, Hand	0	0.75	0.047	4,700

Table 11.2.2. Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimates for Boscalid.

Policy Crop Group Category	Crops	Application Rate[1] (lb ai/A)	Maximum Transfer Coefficient[2] (cm^2/hr)	Activities for Maximum TC	DAT (Day After Treatment)	DFR[5,6,7,8]/TTR[9] Residue (ug/cm^2)	Dose[3] (mg/kg-day)	MOE (LOC = 100)[4]
	Celery; Spinach	0.394	1900	Irrigation (hand set)	0	0.75	0.021	1,000
Vegetable, stem / stalk[5]	Artichoke	0.362	1900	Irrigation (hand set)	0	0.69	0.020	1,100
Vine / trellis[7]	Bushberry; Caneberry	0.362	1900	Irrigation (hand set)	0	1.10	0.031	700
	Grape, wine	0.362	10100	Tying/Training; Harvesting, Hand; Leaf Pulling	0	1.10	0.167	130
	Grape, juice	0.362	10100	Tying/Training; Harvesting, Hand; Leaf Pulling	0	1.10	0.167	130
	Grape, table	0.362	19300	Girdling, Turning	0	1.10	0.32	**69**
					22	0.76	0.003	100
	Grape, raisin	0.362	5500	Tying/Training; Harvesting, Hand; Leaf Pulling	0	1.10	0.091	240

Application rates are the maximum application rates determined from EPA registered labels for boscalid.

2 Transfer Coefficient and Post Application Activities from EPA's Occupational Pesticide Re-entry Exposure Calculator – Revised March 2017.

3 Daily Dermal Dose = [DFR ($\mu g/cm^2$) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption factor (15%)] ÷ BW (80 kg).

4 MOE = POD (22 mg/kg/day) / Daily Dermal Dose.

5 DFR Data source, Tomato DFR study (MRID# 45405302)

6 DFR Data source, Peach DFR study (MRID# 45405304)

7 DFR Data source, Grape DFR study (MRID# 45405303)

8 DFR Data source, Strawberry DFR study (MRID# 45405305)

9 TTR Data source, TTR study (MRID# 45405301)

Restricted-Entry Interval

Boscalid is classified as Toxicity Category III via the dermal route and for skin irritation potential. Dermal sensitization could not be determined. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, in cases where the risks are not of concern at day 0, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to boscalid There were risk estimates of concern related to girdling and turning grapes up to 22 days after applications at 0.362 lb ai/A.

12.0 Incident and Epidemiological Data Review

Boscalid incidents were previously reviewed in 2014 (S. Recore and E. Evans, D418675, 06/25/2014). At that time, based on the low frequency and severity of boscalid incident cases reported to Incident Data System (IDS) and NIOSH Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides further investigation was not warranted.

In the current IDS analysis (S. Recore, D453913, 08/26/2019) from January 1, 2014, to July 10, 2019, no boscalid incidents involving a single active ingredient and three boscalid incidents involving multiple active ingredients were reported to Main IDS; there were two boscalid incidents reported to Aggregate IDS. A query of SENSOR-Pesticides 2011-2015 identified 22 cases involving boscalid.

The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. Boscalid is not included in the AHS, and therefore this study does not provide information for this report.

Based on the continued low frequency and severity of boscalid incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time.

13.0 References

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Donovan, Y., 09/08/2003, D290022. PP# 1F06313 --Human Health Risk Assessment for New Fungicide BAS 510 F (Common Name: Boscalid) -- Proposal for Tolerances for Residues in/on Numerous Crops and Livestock Commodities.

Kidwell, J., 11/14/2002, TXR 0051289. BAS 510 F: Report of the Cancer Assessment Review Committee

S. Recore, 08/26/2019, D453913. Boscalid: Tier I Update Review of Human Incidents and Epidemiology for Draft Risk Assessment

Rury, K., 03/07/2013, TXR 0056585. Boscalid: Summary of Hazard and Science Policy Council (HASPOC) Meeting of February 14,2013: Recommendations on the Waiver Request for the Subchronic Inhalation Study.

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T. Harris, 07/31/2019, D452879. Boscalid Drinking Water Assessment in Support of Registration Review.

L. Bacon, 05/30/2018, D440500 Boscalid. Human Health Risk Assessment of Tolerance Requests for Brassica, Leafy Greens, Subgroup 4-16B; Celtuce; Florence Fennel; Kohlrabi; Leaf Petiole Vegetable Subgroup 22B; Leafy Greens Subgroup 4-16A; Pea and Bean, Dried Shelled, Except Soybean, Subgroup 6C; Pea and Bean, Succulent Shelled, Subgroup 6B; Vegetable, *Brassica*, Head and Stem, Group 5-16, Vegetable, Cucurbit, Group 9; and Vegetable, Root, Except Sugar Beet, Subgroup 1B; and Associated Registration Requests on Greenhouse-grown Fruiting Vegetables, Cucurbit Vegetables, and Leafy Vegetables.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for boscalid are in the table below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1: Toxicology Studies		Required	Submitted	Satisfied
870.1100	Acute Oral Toxicity	yes	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes	yes
870.2400	Acute Eye Irritation	yes	yes	yes
870.2500	Acute Dermal Irritation	yes	yes	yes
870.2600	Skin Sensitization	yes	yes	no[a]
870.3100	90-Day Oral Toxicity in Rodents	yes	yes	yes
870.3150	90-Day Oral Toxicity in Non-Rodents	yes	yes	yes
870.3200	21/28-Day Dermal Toxicity	yes	yes	yes
870.3250	90-Day Dermal Toxicity	no (CR)	no	---
870.3465	90-Day Inhalation Toxicity	yes (CR)	yes	yes
870.3700	Prenatal Developmental Toxicity Study (Rodent)	yes	yes	yes
870.3700	Prenatal Developmental Toxicity Study (Non-Rodent)	yes	yes	yes
870.3800	Reproduction and Fertility Effects	yes	yes	yes
870.4100	Chronic Toxicity (Rodent) 870.4100	yes	yes	yes
	Chronic Toxicity (Non-Rodent)	no	yes	---
870.4200	Carcinogenicity (Two Rodent Species; Rat and Mouse	yes	yes	yes
870.4300	Combined Chronic Toxicity/Carcinogenicity	no	no	yes
870.5100	Bacterial Reverse Mutation Test	yes	yes	yes
870.5300	*in vitro* Mammalian Cell Gene Mutation Test	yes	yes	yes
870.5375	*in vitro* Mammalian Chromosome Aberration Test	yes	yes	yes
870.5385	Mammalian Bone Marrow Chromosomal Aberration Test	---	no	---
870.5395	Mammalian Erythrocyte Micronucleus Test	yes	yes	yes
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	no	yes	---
870.6100	Delayed Neurotoxicity of Organophosphorus Substances (Acute, Hen)	no (CR)	no	---
870.6100	Delayed Neurotoxicity of Organophosphorus Substances (28-Day,	no (CR)	no	---
Hen)		yes	yes	yes
870.6200	Neurotoxicity Screening Battery (Acute, Rat)	yes	yes	yes
870.6200	Neurotoxicity Screening Battery (Subchronic, Rat)	no (CR)	no	---
870.6300	Developmental Neurotoxicity Study			
870.7485	Metabolism and Pharmacokinetics	yes	yes	yes
870.7600	Dermal Penetration	no (CR)	yes	---
870.7800	Immunotoxicity	yes	yes	yes

[a] Submitted study was classified Unacceptable/Nonguideline
CR: Conditionally Required

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity of Boscalid

Table A.2.1. Acute Toxicity Profile – Boscalid (BAS 510 F) Technical.					
Test Material	**Guideline No.**	**Study Type**	**MRID**	**Results**	**Toxicity Category**
Technical	870.1100	Acute Oral - rat	45404814	LD_{50} (M & F) > 5000 mg/kg	IV
Technical	870.1200	Acute Dermal - rat	45404815	LD_{50} (M & F) > 2000 mg/kg	III
Technical	870.1300	Acute Inhalation	45404816	LC_{50} (M & F) > 6.7 mg/L	IV
Technical	870.2400	Primary Eye Irritation	45404817	Not irritating to the eye	IV
Technical	870.2500	Primary Dermal Irritation	45404818	Not irritating to the skin	IV
Technical	870.2600	Dermal Sensitization	46270102	Not a dermal sensitizer	N/A

Table A.2.2. Non-acute Toxicity Profile for Boscalid

Table A.2.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.3100 90-Day oral toxicity rodents (rat)	45404822 (2000) 0, 100, 500, 2000, 5000, 15,000 ppm 0, 7, 34, 137, 347, 1055 mg/kg bw/day Males 0, 8, 40, 159, 395, or 1225 mg/kg bw/day Females Acceptable/Guideline	**NOAEL**: 34/159 mg/kg/day (M/F) **LOAEL**: 137/395 mg/kg/day (M/F): M = increases in absolute and relative thyroid weights and increased incidence of thyroid hyperplasia as well as follicular epithelial hypertrophy; F = increases in absolute and relative thyroid weights.
870.3100 90-Day oral toxicity rodents (mouse)	45404821 (2000) 0, 150, 1000, 4000, 8000 ppm 0, 29, 197, 788, and 1518 mg/kg bw/day Males 0, 42, 277, 1184, and 2209 mg/kg bw/day Females Acceptable/Guideline	**NOAEL**: 197/2209 mg/kg/day (M/F) **LOAEL**: 788/2209 mg/kg/day (M/F): M = increased liver weights and increased incidence of marked fatty change in the liver; F = not attained
870.3150 90-Day oral toxicity in nonrodents (dog)	45404823 (2000) 0, 250, 2500, 25,000 ppm 0, 7.6, 78.1, 728.9 mg/kg/day Males 0, 8.1, 81.7, 824.8 mg/kg/day Females Acceptable/Guideline	**NOAEL**: 7.6/8.1 mg/kg/day (M/F) **LOAEL**: 78.1/81.7 mg/kg/day (M/F): M = increased alkaline phosphatase activity and hepatic weights; F = increased alkaline phosphatase activity and hepatic weights.

Table A.2.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.3200 21/28-Day dermal toxicity (rat)	45404824 (2000) 0, 100, 250, or 1000 mg/kg bw/day Acceptable/Guideline	**NOAEL**: 1000 mg/kg/day (HDT) **LOAEL**: >1000 mg/kg/day
Non-guideline 28-Day inhalation toxicity (rat)	50485703 (2017) 0, 0.025, 0.125, or 0.625 mg/L Acceptable Non-guideline	NOAEC = 0.625 mg/L (equivalent to 625 mg/m^3), highest test dose. LOAEC is not established
870.3700 Prenatal developmental in rodents (rat)	45404904 (2000) 0, 100, 300, 1000 mg/kg bw/day Acceptable/Guideline	**Maternal NOAEL**: 1000 mg/kg/day **Maternal LOAEL**: cannot be established **Developmental NOAEL**: 1000 mg/kg/day **Developmental LOAEL**: cannot be established
870.3700 Prenatal developmental in nonrodents (rabbit)	45404905 (2000) 0, 100, 300, 1000 mg/kg bw/day Acceptable/Guideline	**Maternal NOAEL**: 300 mg/kg/day **Maternal LOAEL**: 1000 mg/kg/day based on abortions or early delivery. **Developmental NOAEL**: 300 mg/kg/day **Developmental LOAEL**: 1000 mg/kg/day based on abortions or early delivery.
870.3800 Reproduction and fertility effects (rat)	45404906 (2001) 0, 100, 1000, 10,000 ppm F_0 premating parental animals M: 10.1, 101.2, 1034.5 mg/kg/day F: 10.7, 106.8,1062.0 mg/kg/day F_1 premating parental animals M: 12.3, 123.9, 1295.4 mg/kg/day F: 12.5, 124.7, 1299.6 mg/kg/day Acceptable/Guideline	**Parental systemic NOAEL**:112.6/1180.8 mg/kg/day (M/F) **Parental systemic LOAEL**:1165.0/>1180.8 mg/kg/day (M/F) decreased body weight (F_1) as well as hepatocyte degeneration F_0 and F_1) in males only. **Offspring systemic NOAEL**:11.2/115.8 mg/kg/day (M/F) **Offspring systemic LOAEL**:112.6/1180.8 mg/kg/day (M/F): decreased body weight for F_2 pups in males and females of both generations. **Reproductive NOAEL**:1165.0/1180.8 mg/kg/day (M/F) **Reproductive LOAEL**:>1165.0/1180.8 (M/F)
870.4100a Chronic toxicity rodents (rat)	45404827, 45723501 (2001) 0, 100, 500, 2500, 15,000 ppm 0, 4.4, 21.9, 110.0, 739.0 mg/kg bw/day for males and 0, 5.9, 30.0, 150.3, 1000.4 mg/kg bw/day for females Acceptable/Guideline	**NOAEL**: 21.9/30.0 mg/kg/day (M/F) **LOAEL**: 110.0/150.3 mg/kg/day (M/F): M = thyroid toxicity (weights and microscopic changes); F = thyroid toxicity (weights and microscopic changes). Thyroid follicular cell adenomas: M = 0/20, 0/20, 2/20,1/20; F = 0/20, 0/20, 1/20,0/20.

Table A.2.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.4100 Chronic toxicity (dog)	45404826 (2000) 0, 200, 800, 2000, 20,000 ppm 0, 5.5, 21.8, 57.4, 544.0 mg/kg bw/day Males 0, 5.8, 22.1, 58.3,592.9 mg/kg bw/day Females Acceptable/Guideline	**NOAEL**: 21.8/22.1mg/kg/day (M/F) **LOAEL**: 57.4/58.3 mg/kg/day (M/F): M = elevated ALP activities and elevated hepatic weights; F = no effects.
870.4200 Carcinogenicity (rat)	45404828 (2001) 0, 100, 500, 2500, 15,000 ppm 0, 4.6, 23.0, 116.1, 768.8 mg/kg bw/day for males and 0, 6.0, 29.7, 155.6, 1024.4 mg/kg bw/day for females) Acceptable/Guideline	**NOAEL**: 23.0/29.7 mg/kg/day (M/F) **LOAEL**: 116.1/155.6 mg/kg/day (M/F): M = increased incidence of thyroid follicular cell hyperplasia and hypertrophy; F = decrease in increased incidence of thyroid follicular cell hyperplasia and hypertrophy. Thyroid follicular cell adenomas: M = 0/50, 0/50, 1/50, 4/50; F = 0/50, 1/50, 0/50, 3/50.
870.4200 Carcinogenicity (mouse)	45404901 (2001) 0, 80, 400, 2000, 8000 ppm 0, 13, 65, 331, 1345 mg/kg bw/day Males 0, 18, 90, 443, 1804 mg/kg bw/day Females) Acceptable/Guideline	**NOAEL**: 65/443 mg/kg/day (M/F) **LOAEL**: 331/1804 mg/kg/day (M/F): M = decreases in body weight; F = decreases in body weight. No evidence of carcinogenicity.
870.5100 Gene Mutation bacterial reverse mutation assay	45404913 (1998) Initial concentrations: 22, 110, 550, 2750, 5500 µg/plate Repeat assay: 20, 100, 500, 2500, 5000 µg/plate Acceptable/Guideline	Negative without and with S-9 activation up to limit dose of 5000 µg/plate.
870.5300 *In vitro* mammalian cell forward gene mutation assay (CHO cells/HGPRT locus)	45404914 (2000) Initial concentrations: 15.625, 31.25, 62.5, 125, 250 or 500 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix) Repeat concentrations: 10.24, 25.6, 64, 160, 400 1000 µg/mL with and without S9-mix with a repeat of the non-activated test at concentrations of	Negative without and with S-9 activation up to the limit of solubility of 25 µg/mL.

Table A.2.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
	3.125, 6.25, 12.5, 25, 50, 100 µg/mL Acceptable/Guideline	
870.5375 *In vitro* mammalian cytogenetics assay in Chinese hamster V79 cells	45404915 (1999) Initial exposure: 0, 20.0, 100.0 500.0 µg/mL with and without metabolic activation Second exposure: 0, 31.25, 62.5, 125.0 µg/mL in the absence of S9-mix Acceptable/Guideline	Negative without and with S-9 activation up to 3500 µg/mL with precipitation showing at concentrations of 100 µg/mL and higher.
870.5395 Cytogenetics - mammalian erythrocyte micronucleus test in the mouse	45404916 (1999) 0, 500, 1000, 2000 mg/kg bw Acceptable/Guideline	Negative at doses up to 2000 mg/kg.
870.5500 *In vitro* unscheduled DNA synthesis (primary rat hepatocytes)	45404917 (2000) First: 0, 5, 10, 50, 100, 250, 500, 750, 1000 µg/mL Repeat due to excess cytotoxicity: 0, 0.5, 1.0, 5.0, 10.0, 50.0, 100.0, 250.0, 500.0 µg/mL A second experiment was conducted at 1.563, 3.125, 6.250, 12.500, 25.000, 50.000 µg/mL Acceptable/Guideline	Negative response up to 50 µg/mL. Cytotoxicity at 100-500 µg/mL.
870.6200a Acute neurotoxicity screening battery (rat)	45404820 (2000) 0, 500, 1000 or 2000 mg/kg bw Acceptable/Guideline	**NOAEL**:2000/1000 mg/kg/day (M/F) **LOAEL**: >2000/2000 mg/kg/day (M/F): F = piloerection
870.6200b Subchronic neurotoxicity screening battery (rat)	45404825 (2001) 0, 150, 1500, 15000 ppm 0, 10.5, 103.1 1050.0 mg/kg bw/day for males 0, 12.7, 124.5 or 1272.5 mg/kg bw/day for females Acceptable/Guideline	**NOAEL**:1050.0/1272.5 mg/kg/day (M/F) **LOAEL**: >1050.0/1272.5 mg/kg/day (M/F)

Table A.2.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.6300 Developmental neurotoxicity (rat)	45404907 (2001) 45800101 (2002) 45800102 (2002) 0, 100, 1000 10000 ppm 0, 14, 147 1442 mg/kg/day Acceptable/Guideline	**Maternal NOAEL:**1442 mg/kg/day **Maternal LOAEL:** >1442 mg/kg/day **Offspring NOAEL:** 14 mg/kg/day **Offspring LOAEL:** 147 mg/kg/day (decreased body weights on PND 4.
870.7485 Metabolism and pharmacokinetics (rat)	45404918 (2001) 45404919 (2000) 45692401 (2002) a single 50 or 500 mg/kg oral dose, or a 14-day repeated dose (500 mg/kg/day) Acceptable/Guideline	BAS 510 F was readily absorbed and excreted following single oral 50 mg/kg; at single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion mainly by feces (80-98%). Biliary excretion 40-50% of fecal activity at 50 mg/kg, 10% at 500 mg/kg. Urine, about 16% at 50 mg/kg, 3-5% at 500 mg/kg. Absorption about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns similar by gender or radiolabel position. Metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with glucuronic acid or sulfate, or by conjugation of the parent with glutathione with cleavage to sulfate metabolites.
870.7600 Dermal Penetration (rat)	45404920 (2001) 0.01, 0.10, 1.0 mg/cm^2 for 1, 4, 10, or 24 hours Acceptable/Guideline	Maximum % absorption: 0.01 mg/cm^2 = 10.93 (24 hour exposure, 24 hour sacrifice) 0.10 mg/cm^2 = 3.76 (24 hour exposure, 24 hour sacrifice) 1.00 mg/cm^2 = 1.48 (10 hour exposure, 72 hour sacrifice)
870.7800 Immunotoxicity (rat)	MRID 48203801 (2003) 0, 100, 1000, or 10000 ppm 0, 7.45, 73.1, or 736.2 mg/gk/day Acceptable / Guideline	NOAEL = 736.2 mg/kg/day LOAEL = not established
Non-guideline Hepatic enzyme induction (rat)	45404902 (1999) 0 or 15,000 ppm (equivalent to 0 or ~1500 mg/kg bw/day) for two weeks Acceptable/Non-guideline	1. hypertrophy of zone III hepatocytes 2. >20% increase in liver weight 3. increase in CYP450 activity 4. slight to extensive microscopic SER proliferation 5. not a peroxisome proliferator 6. enzymes in CYP450 subfamily not induced 7. no notable microscopic increase in size or number of peroxisomes CONCLUSION: inducer of total CYP450 activity

Table A.2.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
Non-guideline Hormone and enzyme induction (rat)	45404903 (2001) 0 or 15,000 ppm 0 or ~1000 mg/kg bw/day For four weeks Acceptable/Non-guideline	1. slight (statistically significant) decrease in circulating T_3 and T_4 only in males 2. increase in circulating TSH levels both sexes 3. increase in all 3 liver microsomal glucuronyltransferases CONCLUSION: disruption of thyroid homoeostasis by decreasing circulating T_3 and T_4 and increasing TSH; likely the result of hepatic microsomal glucuronyltransferase induction
Non-guideline Reversibility study (dietary): 4-week administration followed by 4 weeks recovery or 13 weeks recovery (rat)	45550601 (2001) 0, 100, 2500, 15000 ppm 0, 7.7, 190.3, 1137.4 mg/kg/day) Acceptable/Non-guideline	4 weeks dosing: at 2500 and 15000 ppm: increase in TSH (68% and 87%); increase in absolute and relative thyroid weights, hypertrophy of thyroid follicular epithelial cells and diffuse follicular hyperplasia, increase in absolute and relative liver weights and centrilobular hypertrophy as well as liver portal fatty changes. 4 weeks dosing + 4 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. 4 weeks dosing + 13 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. CONCLUSION: induction of liver microsomal enzyme system resulting in increased glucuronidation of thyroxine, resulting in an increase in TSH secretion as a compensatory response of the physiological negative feedback system; increased TSH resulted in increased thyroid weight.

Appendix A.3 Executive Summaries

EXECUTIVE SUMMARY: In a 28-day subchronic inhalation toxicity study (MRID 50485703, groups of ten Wistar [Crl:WI(Han)] rats/sex/concentration were exposed to boscalid (98.9% a.i.; batch # COD-001415) by nose-only inhalation at concentrations of 0 (air control), 0 (vehicle control), 0.025, 0.125, or 0.625 mg/L (equivalent to 0, 0, 25, 125, and 625 mg/m^3) 6 h/day, 5 days/week, for a total of 20 exposures. AEROSIL® R 972 (0.006 mg/L) was added to the treatment groups to improve the flow and enable generation of a dust aerosol; a vehicle control group exposed to AEROSIL only was included.

There were no effects of treatment on mortality, clinical signs, body weights or body weight gains, food consumption, ophthalmoscopic examinations, neurobehavioral assessments, hematology, clinical chemistry, organ weights, or gross or microscopic pathological findings.

The systemic LOAEC was not observed. The systemic NOAEC is 0.625 mg/L (equivalent to 625 mg/m^3).

Systemic and port-of-entry findings were attributed to exposure to the vehicle control substance, AEROSIL® R 972. The following findings were reported for the vehicle control group in comparison to the air control group. The males lost weight during Days 0-4 and 7-11, and 21-25, resulting in a 6-7% decrease in body weights during Days 11-28. Absolute neutrophil counts were increased by 54% in males and by 76% in females. Relative neutrophil counts were increased by 53% and relative lymphocyte counts were decreased by 11% in the males; and relative neutrophil counts were increased by 31% and relative lymphocyte counts were decreased by 8% in the females. Terminal body weights were decreased by 7% in the males. Increases in absolute (↑31% and ↑43%) and relative (↑42% and ↑45%) lung weights were noted in the males and females, respectively. Enlarged mediastinal lymph nodes were observed in 10/10 males and females. Microscopically, moderate to marked multifocal, mixed-cell inflammation of the lungs was observed in 10/10 males, with minimal to moderate macrophage aggregates in the BALT noted in 9/10 males. In the mediastinal lymph nodes, slight to moderate lymphoreticular hyperplasia was observed in 9/10 males, and slight to marked macrophage aggregation comparable to that observed in the BALT of the lungs was noted in 9/10 males. In the tracheobronchial lymph nodes, minimal to moderate lymphoreticular hyperplasia was observed in 6/10 males, and minimal to marked macrophage aggregation was noted in 10/10 males. Slight to marked multifocal, mixed-cell inflammation of the lungs was observed in 10/10 females, and minimal to moderate macrophage aggregates were noted in 6/10 females in the BALT. In the mediastinal lymph nodes, minimal to marked lymphoreticular hyperplasia was observed in 10/10 females, and minimal to marked macrophage aggregation was noted in 10/10 females. In the tracheobronchial lymph nodes, slight lymphoreticular hyperplasia was observed in 2/10 females, and minimal to moderate macrophage aggregation was noted in 10/10 females.

Additional gross and microscopic findings were noted in the treated groups. Enlarged mediastinal lymph nodes were observed in 4/10 males and 6/10 females at 0.125 mg/L and in 5/10 males and 10/10 females at 0.625 mg/L. In the males, multifocal, mixed-cell inflammation of the lungs was observed in 10/10 rats at 0.125 mg/L (minimal to slight) and in 10/10 rats at 0.625 mg/L (moderate to marked). In the BALT of the lungs, minimal to moderate macrophage aggregates were noted in 3/10 rats at 0.625 mg/L. In the mediastinal lymph nodes, lymphoreticular hyperplasia was observed in 4/10 rats at 0.125 mg/L (slight), and in 10/10 rats at 0.625 mg/L (minimal to moderate), and macrophage aggregation was noted in 5/10 rats at 0.125 mg/L (minimal) and in 10/10 rats at 0.625 mg/L (minimal to moderate). In the tracheobronchial lymph nodes, minimal to moderate lymphoreticular hyperplasia was observed in 8/10 rats at 0.625 mg/L, and macrophage aggregation was noted in 5/10 rats at 0.125 mg/L (minimal to slight) and in 10/10 rats at 0.625 mg/L (minimal to moderate). In the females, multifocal, mixed-cell inflammation of the lungs was observed in 10/10 rats at 0.125 mg/L (slight to moderate) and in 10/10 rats at 0.625 mg/L (moderate to marked). In the BALT of the lungs, macrophage aggregates were noted in 1/10 rats at 0.125 mg/L (slight) and in 5/10 rats at 0.625 mg/L (slight to moderate). In the mediastinal lymph nodes, lymphoreticular hyperplasia was observed in 5/10 rats at 0.125 mg/L (minimal to slight) and in 9/10 rats at 0.625 mg/L (minimal to moderate), and macrophage aggregation was noted in 5/10 rats at 0.125 mg/L (minimal to marked), and 10/10 rats at 0.625 mg/L (minimal to moderate). In the

tracheobronchial lymph nodes, slight lymphoreticular hyperplasia was observed in 1/10 rats at 0.625 mg/L, and macrophage aggregation was noted in 6/10 rats at 0.125 mg/L (minimal to moderate) and in 10/10 rats at 0.625 mg/L (slight to moderate). These findings were attributed to exposure to the vehicle control, and were not considered to have resulted from treatment.

The inhalation LOAEC was not observed. The inhalation NOAEC is 0.625 mg/L (equivalent to 625 mg/m^3). Exposure to the vehicle control substance (0.006 mg/L) caused body weight losses in the males, alterations in hematology parameters, and gross and microscopic findings in the lungs and lymph nodes.

This study is classified **acceptable / non-guideline**. It generally satisfied the guideline requirements OECD 412 (Subchronic inhalation toxicity; 28-day study; October 9, 2017) in the rat, with the exception that bronchoalveolar lavages were not performed.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided. It was stated that this study was conducted in accordance with the OECD Principles of Good Laboratory Practice and the GLP Principles of the German "Chemikaliengesetz" (Chemicals Act) which meet the United States Environmental Protection Agency Good Laboratory Practice Standards ([40 CFR Part 160 (FIFRA) and Part 792 (TSCA)], with the exception that recognized differences exist between the GLP Principles/Standards of OECD and the Principles/Standards of FIFRA and TSCA

Appendix A.4 Literature Search for Boscalid

Date and Time of Search: 04/16/2019; 03:30 pm
Search Details:
((*Boscalid*)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed hits: 29
Number of Swift Articles: 11 for Animal
Number of Swift Articles: 21 for Human
Number of Swift Articles: 0 for No Tag

Appendix B. Physical/Chemical Properties

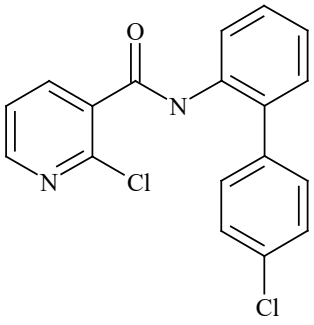
Table B.1. Nomenclature of Boscalid.	
Compound	
Common name	Boscalid;
Company experimental name	BAS 510 F
IUPAC name	2-chloro-*N*-(4′-chlorobiphenyl-2-yl)nicotinamide
CAS name	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide
Molecular weight	343.2
CAS registry number	188425-85-6
End-use product (EPs)	Pristine® Fungicide, EPA Reg. No. 7969-199 Endura® Fungicide, EPA Reg. No. 7969-197 Pagent Intrinsic, EPA Reg No. 7969-251

Table B.2. Physicochemical Properties of Boscalid.		
Parameter	Value	References
Melting point/range	142.8-143.8 □C	MRIDs 45404802 and 45404804-45404809
pH	NA (does not dissociate in water)	
Relative Density (20ºC)	1.381g/cm^3	
Water solubility (20ºC)	4.64 mg/L at pH 6	
Solvent solubility (g/100 mL at 20ºC)	acetone 16-20; ethyl acetate 6.7-8.0 methanol 4-5; 2-propanol <0.01 acetonitrile 4-5; dichloromethane 20-25 toluene 2-5; n-heptane <0.01 1-octanol <0.01; olive oil 2.9 N,N-DMF >25	
Vapor pressure	7 x 10^{-9} hPa	
Dissociation constant, pK$_a$	None (does not dissociate in water)	
Octanol/water partition coefficient, Log(K$_{OW}$)	2.96	
UV/visible absorption spectrum	UV molecular extinction (e[lmol^{-1}cm^{-1}]): 3.15 x10^4 at 228 nm; 1.53 x10^3 at 290 nm	

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1; the AHETF database; the Outdoor Residential Exposure Task Force (ORETF) database; the ARTF database; are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[11].

[11] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix D. International Residue Limit Status Sheet.

Summary of US and International Tolerances and Maximum Residue Limits			
Residue Definition:			
US		Canada	Codex[2]
40 CFR §180.589 (a)(1) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′ -chloro[1,1'-biphenyl]-2-yl)		2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide	Boscalid. The residue is fat soluble.
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*		
	US	Canada	Codex[3]
Alfalfa, forage	30		
Alfalfa, hay	65		
Almond, hulls	15		15
Apple, wet pomace	10		
Artichoke, globe	6		30
Avocado	2	2	
Banana[4]	0.6	0.6	0.6
Berry, low growing, subgroup 13-07G, except cranberry	4.5	4.5	3 (strawberry) 10-all other berries
Brassica, leafy greens, subgroup 4-16B, except watercress	60	50	40
Bushberry subgroup 13-07B	13	11	10 (berries and small fruits)
Caneberry subgroup 13-07A	10	6	10 (berries and small fruits)
Canistel	1.5		
Coffee, green bean[1]	0.05	0.05	0.05
Cotton, gin byproducts	55		
Dill, seed	100		
Endive, Belgian	6	6	30
Fennel, florence, fresh leaves and stalk	45	45	
Fruit, citrus, group 10-10	2	3	2
Fruit, citrus, group 10-10, dried pulp	4.5		
Fruit, citrus, group 10-10, oil	85	85	
Fruit, pome, group 11-10	3	3	2 pome fruits Proposed
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	5	3.5	5 (grape)
Fruit, stone, group 12-12	5	1.7	4 subgroup of peaches 1.5 subgroup of plums 5 subgroup of cherries (all proposed)
Grain, aspirated fractions	3		
Grape, raisin	8.5	8.5	
Herb subgroup 19A	150		
Hop, dried cones	35	35	60
Kohlrabi	6		5
Leaf petiole vegetable subgroup 22B	45	45	30
Leafy greens subgroup 4-16A	70	60	40
Mango	2	2	
Nut, tree, group 14-12	0.7	0.7	0.05 1 pistachio

Summary of US and International Tolerances and Maximum Residue Limits			
Residue Definition:			
US		Canada	Codex[2]
40 CFR §180.589 (a)(1) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′ -chloro[1,1'-biphenyl]-2-yl)		2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide	Boscalid. The residue is fat soluble.
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*		
	US	Canada	Codex[3]
Oilseed group 20	3.5	3.5 Rapeseed subgroup 20A 1.6 Sunflower subgroup 20B 0.05 Cottonseed subgroup 20C	1 (oilseeds)
Papaya	2	2	
Peanut	0.05	0.05	1
Peanut, meal	0.15		
Peanut, refined oil	0.15	0.15	
Peppermint, fresh leaves	30	30	
Persimmon	8		
Rapeseed subgroup 20A, oil	5	5	
Sapodilla	1.5		
Sapote, black	1.5		
Sapote, mamey	1.5		
Soybean, hulls	0.2		
Soybean, seed	0.1	0.1	3
Soybean, vegetable	2	1.6	
Spearmint, leaves	30	30	
Star apple	1.5		
Vegetable, Brassica, head and stem, group 5-16	6	6	5
Vegetable, bulb, group 3-07	5	3	5
Vegetable, cucurbit, group 9	3	1.5 melon subgroup 9A 0.5 cucumber, Chinese cucumber 1.5 balsam apples, balsam pear, chayote fruit, chinese wax gourds, edible gourds , pumpkin, summer squash, winter squash	3
Vegetable, fruiting, group 8-10	3	1.4	3
Vegetable, legume, dried shelled, except soybean, subgroup 6C	3	2.5	3
Vegetable, legume, edible podded, subgroup 6A	5	1.6	
Vegetable, legume, succulent shelled, subgroup 6B	0.6	0.6	3

Summary of US and International Tolerances and Maximum Residue Limits		
Residue Definition:		
US	Canada	Codex[2]
40 CFR §180.589 (a)(1) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′ -chloro[1,1'-biphenyl]-2-yl)	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide	Boscalid. The residue is fat soluble.

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*		
	US	Canada	Codex[3]
Vegetable, root, except sugar beet, subgroup 1B	2	1 garden beet, turnip roots 0.7	2
Vegetable, tuberous and corm, subgroup 1C	0.05	0.05	

[1] Includes all commodities with current US tolerances. [2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Summary of US and International Tolerances and Maximum Residue Limits		
Residue Definition:		
US	Canada	Codex[2]
40 CFR §180.589 (a)(2) (2) Compliance with the tolerance levels specified below is to be determined by measuring only the sum of boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4′ -chloro[1,1′-biphenyl]-2-yl), and metabolites 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide and glucuronic acid conjugate of 2-chloro-N-(4′-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide, calculated as the stoichiometric equivalent of boscalid	2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide, including the metabolites 2-chloro-N-(4'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide and the glucuronic acid conjugate of 2-chloro-N-(4'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide (expressed as parent equivalent	Boscalid. The residue is fat soluble.

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*		
	US	Canada	Codex[3]
Cattle, fat	0.3	0.3	
Cattle, meat	0.1	0.1	0.7
Cattle, meat byproducts	0.35	0.35	0.2
Egg	0.02	0.02	0.02
Goat, fat	0.3	0.3	
Goat, meat	0.1	0.1	0.7
Goat, meat byproducts	0.35	0.35	0.2
Hog, fat	0.2	0.3	
Hog, meat	0.05	0.1	0.7
Hog, meat byproducts	0.1	0.35	0.2
Horse, fat	0.3	0.3	
Horse, meat	0.1	0.1	0.7
Horse, meat byproducts	0.35	0.35	0.2
Milk	0.1	0.1	0.1
Poultry, fat	0.2	0.05	0.02
Poultry, meat	0.05	0.05	0.02

Summary of US and International Tolerances and Maximum Residue Limits		
Residue Definition:		
US	Canada	Codex[2]
40 CFR §180.589 (a)(2) (2) Compliance with the tolerance levels specified below is to be determined by measuring only the sum of boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4′-chloro[1,1′-biphenyl]-2-yl), and metabolites 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide and glucuronic acid conjugate of 2-chloro-N-(4′-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide, calculated as the stoichiometric equivalent of boscalid	2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide, including the metabolites 2-chloro-N-(4'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide and the glucuronic acid conjugate of 2-chloro-N-(4'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide (expressed as parent equivalent	Boscalid. The residue is fat soluble.

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*		
	US	Canada	Codex[3]
Poultry, meat byproducts	0.2	0.1	0.02
Sheep, fat	0.3	0.3	
Sheep, meat	0.1	0.1	0.7
Sheep, meat byproducts	0.35	0.35	0.2

Summary of US and International Tolerances and Maximum Residue Limits		
Residue Definition:		
US	Canada	Codex[2]
40 CFR §180.589 (d) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′ -chloro[1,1'-biphenyl]-2-yl)	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide	Boscalid. The residue is fat soluble.

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*		
	US	Canada	Codex[3]
Animal feed, nongrass, group 18, forage, except alfalfa	1		
Animal feed, nongrass, group 18, hay, except alfalfa	2		
Animal feed, nongrass, group 18, seed	0.05		
Beet, sugar, roots	0.1	1	
Grain, cereal, forage, fodder, and straw, group 16, forage	2		
Grain, cereal, forage, fodder, and straw, group 16, stover	1.5		
Grain, cereal, forage, fodder, and straw, group 16, straw	3		50 wheat straw
Grain, cereal, group 15	0.2	0.2	0.1 corn, pop, sweet, sorghum, and teff 0.5 barley, oats, rye, and wheat
Grass, forage, fodder and hay, group 17, forage	2		
Grass, forage, fodder and hay, group 17, hay	8		

Summary of US and International Tolerances and Maximum Residue Limits		
Residue Definition:		
US	Canada	Codex[2]
40 CFR §180.589 (d) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′ -chloro[1,1'-biphenyl]-2-yl)	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide	Boscalid. The residue is fat soluble.

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*		
	US	Canada	Codex[3]
Grass, forage, fodder and hay, group 17, seed screenings	0.2		
Grass, forage, fodder and hay, group 17, straw	0.3		
Rice, hulls	0.5		
Vegetable, foliage of legume, group 7, forage	1.5		
Vegetable, foliage of legume, group 7, hay	2		
Vegetable, foliage of legume, group 7, vines	0.05		
Vegetable, leaves of root and tuber, group 2	0.1	1	40

[1] Includes all commodities with current US tolerances.[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix E. Summary of Directions for Agricultural Occupational and Residential Uses of Boscalid

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
12-12. Stone Fruit Group	7969-199	Dry Flowable	● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/ Overhead irrigation	0.228 lb ai/A	1.14 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
19A. Herb subgroup	7969-199	Dry Flowable	● Banded ● Broadcast ● Directed	● Groundboom sprayer	0.291 lb ai/A	0.583 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Aerial ● Drip irrigation ● Irrigation equipment
1C. Tuberous and corm vegetables subgroup	7969-197	Dry Flowable	● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/ Overhead irrigation	0.438 lb ai/A	0.875 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	10	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
Alfalfa	7969-197	Dry Flowable	● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/ Overhead irrigation	0.481 lb ai/A	0.963 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Almond	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.232 lb ai/A	0.928 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	25	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/ Overhead irrigation							
Artichoke	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.09 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Beans, Dried-type	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.481 lb ai/A	0.963 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-	21	Restricted Site/Loc: ● Agricultural (Indoor)
			● Broadcast	● Aerial ● Groundboom sprayer ●							

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
				Sprinkler/Overhead irrigation					sleeve shirt, long pants, shoes/socks ● Protective Eyewear		Restricted Equipment: ● Drip irrigation
Beans, Succulent (Snap)	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.481 lb ai/A	0.963 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	7	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Blueberry	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.45 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Brassica (Head and Stem) Vegetables	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000809 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Equipment: ● Seed treatment, on farm
	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant	0	Restricted Site/Loc:

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation					gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear		● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Bulb Vegetables	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000809 lb / lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● Seed treatment, on farm
	7969-197	Dry Flowable	● Banded ● Directed ● In-furrow	● Groundboom sprayer	0.298 lb ai/A	1.79 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	7	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Bushberries; Caneberries	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.45 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt,	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment:
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
									long pants, shoes/socks		● Drip irrigation
Canola/Rape	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000809 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Equipment: ● Seed treatment, on farm
	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.263 lb ai/A	0.525 lb ai/A	NS	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	21	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Carrot (including tops); Celeriac	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.341 lb ai/A	1.02 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
Celery	7969-197	Dry Flowable	● Banded ● Directed ● Broadcast	● Groundboom sprayer ● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Citrus	7969-199	Dry Flowable	● Banded ● Directed ● Broadcast	● Groundboom sprayer ● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation	0.291 lb ai/A	1.17 lb ai/A	10	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Coniferous/Evergreen/Softwood (non-food)	7969-251	Dry Flowable	● Broadcast ● Banded	● Backpack sprayers ● Groundboom sprayer ● Manually pressurized hand sprayer ● Mechanically pressurized hand sprayer	0.284 lb ai/A	1.86 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
	7969-196	Dry Flowable	● Broadcast	● Groundboom sprayer	0.70 lb ai/A	2.10 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer	NS	Restricted Site/Loc: ● NS Restricted Equipment:

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
									● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear		● Irrigation equipment
	7969-251	Dry Flowable	● Broadcast	● Aerial	0.284 lb ai/A	1.86 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
Cotton	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	30	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000809 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Equipment: ● Seed treatment, on farm

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
Crops grown for oil	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.263 lb ai/A	0.525 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	21	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Cucurbit Vegetables	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000809 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Equipment: ● Seed treatment, on farm
	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.291 lb ai/A	1.17 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
Deciduous/Broadleaf/Hardwood (non-food)	7969-251	Dry Flowable	● Broadcast● Banded	● Backpack sprayers ● Groundboom sprayer ● Manually pressurized hand sprayer ● Mechanically pressurized hand sprayer	0.284 lb ai/A	1.86 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
	7969-196	Dry Flowable	● Broadcast	● Groundboom sprayer	0.70 lb ai/A	2.10 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● Irrigation equipment
	7969-251	Dry Flowable	● Broadcast	● Aerial	0.284 lb ai/A	1.86 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
Dill	7969-199	Dry Flowable	● Banded ● Broadcast ● Directed	● Groundboom sprayer	0.291 lb ai/A	0.583 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Aerial ● Drip irrigation ● Irrigation equipment
Endive (Escarole)	7969-199	Dry Flowable	● Spray Drench	● Conveyor application system	0.0000284 lb ai/lb root	NS	NS	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	19	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Fruiting Vegetables	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.153 lb ai/A	0.919 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Ginseng	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.341 lb ai/A	1.02 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt,	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment:
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
									long pants, shoes/socks ● Protective Eyewear		● Drip irrigation
Grapes	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.09 lb ai/A	10	● See Issues	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Grass/Turf: golf course	7969-196	Dry Flowable	● Broadcast	● Groundboom sprayer	0.35 lb ai/A; 0.00402 lb ai/gal	2.10 lb ai/A	14	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	NS	Restricted Site/Loc: ● Agricultural (Outdoor) Restricted Equipment: ● Irrigation equipment
Hops	7969-199	Dry Flowable	● Broadcast	● Aerial	0.221 lb ai/A	NS	10	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Banded ● Directed	● Groundboom sprayer	0.441 lb ai/A;	1.32 lb ai/A	10	12 hr	● Chem. resistant	14	Restricted Site/Loc:

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
			● Broadcast	● Groundboom sprayer ● Sprinkler/Overhead irrigation	0.00221 lb ai/gal				gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks		● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Horseradish	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.341 lb ai/A	1.02 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Leaf petioles (except brassica)	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
				● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Leafy Brassica greens; Leafy greens (except brassica)	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
									● Protective Eyewear		
Legume Vegetables	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000404 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Equipment: ● Seed treatment, on farm
Lettuce	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.481 lb ai/A	0.963 lb ai/A	NS	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Low Growing Berries	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.81 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Ornamentals	7969-196	Dry Flowable	● Banded	● Groundboom sprayer	0.70 lb ai/A	2.10 lb ai/A	7	12 hr	● Chem. resistant	NS	Restricted Site/Loc:

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
			● Broadcast	● Backpack sprayers ● Groundboom sprayer ● Manually pressurized hand sprayer ● Mechanically pressurized hand sprayer	0.70 lb ai/A; 0.007 lb ai/gal	2.10 lb ai/A	7	12 hr	gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear		● NS Restricted Equipment: ● NS
			● Dip Treatment	● Dip tank	0.70 lb ai/ 100 gal	NS	NS	12 hr			
			● Broadcast	● Aerial ● Sprinkler/Overhead irrigation ● Drip irrigation	0.70 lb ai/A	2.10 lb ai/A	7	12 hr			
	499-553	RTU	● Fumigation: Enclosed spaces	● Total-release fogger	0.192 lb ai/A	0.66 lb ai/A	7	● See Issues	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
	7969-353	Flowable Concentrate	● Broadcast	● Hose-end sprayer ● Manually pressurized hand sprayer	0.326 lb ai/A; 0.00326 lb ai/gal	NS	14	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
Peanuts	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.441 lb ai/A	1.32 lb ai/A	14	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
											irrigation
Peas, Dried-type	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.481 lb ai/A	0.963 lb ai/A	5	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	21	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Peas, Succulent	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.481 lb ai/A	0.963 lb ai/A	5	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	7	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Persimmon	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.09 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Pistachio	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.228 lb ai/A	0.914 lb ai/A	10	12 hr	● Chem. resistant	14	Restricted Site/Loc:

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation					gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks		● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Pome Fruits	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.291 lb ai/A	1.17 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Potato, White/Irish (or unspecified)	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.438 lb ai/A	0.875 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	10	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Roquette (Arugula)	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000809 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Equipment: ● Seed treatment, on farm

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
Skirret	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.341 lb ai/A	1.02 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Small Fruits	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.09 lb ai/A	10	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Soybeans	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.481 lb ai/A	0.963 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	21	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000404 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ●	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● Seed

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
									Respirator, NIOSH filtering half face		treatment, on farm
Spinach	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Stone Fruits	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.232 lb ai/A	1.16 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Strawberry	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.362 lb ai/A	1.81 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Subtropical/Tropical Fruits	7969-199	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.291 lb ai/A	0.583 lb ai/A	7	12 hr	● Chem. resistant	0	Restricted Site/Loc:

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid

Use Site	EPA REG Number	Formulation Type	App. Type	Application Equipment	Maximum Single Application Rate	Maximum Application Rate per Year	MRI (days)	REI	PPE	PHI (days)	Method Restrictions
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation					gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks		● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
Sunflower	7969-274	Flowable Concentrate	● Seed/Seed Piece treatment	● Seed treatment, commercial	0.000404 lb ai/lb seed	NS	NS	● NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● Seed treatment, on farm
	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	21	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Tomato	7969-251	Dry Flowable	● Broadcast	● Backpack sprayers ● Groundboom sprayer ● Manually pressurized hand sprayer ● Mechanically pressurized hand sprayer ● Mist-blower	0.362 lb ai/A; 0.00362 lb ai/gal	1.09 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ●	0	Restricted Site/Loc: ● NS Restricted Equipment: ● NS

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
									Respirator, NIOSH filtering half face		
	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.547 lb ai/A; 0.00547 lb ai/gal	1.09 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	0	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Tree Nuts	7969-197	Dry Flowable	● Banded ● Directed	● Groundboom sprayer	0.232 lb ai/A	0.928 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Drip irrigation
			● Broadcast	● Aerial ● Groundboom sprayer ● Sprinkler/Overhead irrigation							
Turnip (Greens)	7969-197	Dry Flowable	● Banded ● Broadcast ● Directed	● Groundboom sprayer	0.394 lb ai/A	0.788 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks	14	Restricted Site/Loc: ● Agricultural (Indoor) Restricted Equipment: ● Aerial ● Center

Table E.1. Summary of Directions for Agricultural Occupational Uses of Boscalid											
Use Site	**EPA REG Number**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
									● Protective Eyewear		pivot sprinkler irrigation ● Drip irrigation ● Lateral move sprinkler irrigation ● Solid set sprinkler irrigation ● Wheel line/Linear sprinkler irrigation sprinkler

Table E.2. Summary of Directions for Residential Uses of Boscalid											
Use Site	**Representative Formulation**	**Formulation Type**	**App. Type**	**Application Equipment**	**Maximum Single Application Rate**	**Maximum Application Rate per Year**	**MRI (days)**	**REI**	**PPE**	**PHI (days)**	**Method Restrictions**
Turf	7969-196	Dry Flowable	● Broadcast	● Groundboom sprayer	0.35 lb ai/A; 0.00402 lb ai/gal	2.10 lb ai/A	14	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	NS	Restricted Site/Loc: ● Agricultural (Outdoor) Restricted Equipment: ● Irrigation equipment
Ornamentals	7969-196	Dry Flowable	● Broadcast ● Banded	● Backpack sprayers ● Groundboom sprayer ● Manually pressurized hand sprayer ● Mechanically pressurized hand sprayer	0.70 lb ai/A; 0.007 lb ai/gal	2.10 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS

	7969-251	Dry Flowable	● Broadcast ● Banded	● Backpack sprayers ● Groundboom sprayer ● Manually pressurized hand sprayer ● Mechanically pressurized hand sprayer	0.284 lb ai/A	1.86 lb ai/A	7	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Respirator, NIOSH filtering half face	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
	7969-196	Dry Flowable	● Dip Treatment	● Dip tank	0.70 lb ai/100 gal	NS	NS	12 hr	● Chem. resistant gloves ● Coverall / Double-layer ● Long-sleeve shirt, long pants, shoes/socks ● Protective Eyewear	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
	7969-353	Flowable Concentrate	● Broadcast	● Hose-end sprayer ● Manually pressurized hand sprayer	0.326 lb ai/A; 0.00326 lb ai/gal	NS	14	NS	● Chem. resistant gloves ● Long-sleeve shirt, long pants, shoes/socks	NS	Restricted Site/Loc: ● NS Restricted Equipment: ● NS
	4-488	Flowable Concentrate	Broadcast	Hose-end sprayer ● Manually pressurized hand sprayer Back pack sprayer	0.0076 lb ai/gal	NS	14	NS	None	5-25	Restricted Site/Loc: ● NS Restricted Equipment: ● NS

Derivation of Proposed Groundwater

Interim Maximum Allowable Concentration (IMAC)

Fluometuron

1. Introduction

North Carolina regulations [15A NCAC 02L.0202 (c)] allow a party to petition for the establishment of an Interim Maximum Allowable Concentration (IMAC) for a substance lacking a groundwater standard. In the absence of a groundwater standard for fluometuron, an IMAC is proposed in this document. The IMAC was developed in accordance with the North Carolina Department of Environmental Quality (NCDEQ) Division of Water Resources Standard Operating Procedure for Establishing IMACs (NCDEQ, 2022).

Per the regulations [15A NCAC 02L.0202 (c)], the groundwater quality standard (GWQS) is the lowest of the following:

1. Systemic threshold concentration;
2. Concentration corresponding to an incremental lifetime cancer risk of 10^{-6};
3. Taste threshold limit value;
4. Odor threshold limit value;
5. Maximum contaminant level (MCL);
6. National secondary drinking water standard.

The regulations [15A NCAC 02L.0202 (c)] state that the following sources, in order of preference, be used in establishing the above levels:

1. The United States Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS).
2. Health Advisories (USEPA Office of Drinking Water).
3. Other health risk assessment data published by USEPA.
4. Other relevant, published health risk assessment data, and scientifically valid peer-reviewed published toxicological data.

Section 2 provides an overview of fluometuron and a summary of available data. Risk-based GWQS are calculated in Section 3, and the proposed IMAC is presented in Section 4. References are provided in Section 5.

2. Fluometuron Data

Fluometuron (CAS No. 2164-17-2) is a registered herbicide used to control broadleaf weeds and grasses in cotton crops. It is a white crystalline odorless powder. The chemical structure and chemical properties are provided in **Attachment A** (PubChem, 2023).

An oral reference dose (RfD) of 0.013 milligrams per kilogram body weight per day (mg/kg-day) is available from IRIS (USEPA, 2023a) for fluometuron. The RfD is based on a 103-week oral feeding study

in rats. No observed effects were identified at the highest dose of 12.5 mg/kg-day, which was selected as the no observed adverse effect level (NOAEL). USEPA applied uncertainty factors of 10 for interspecies extrapolation, 10 for intraspecies extrapolation, and 10 for the lack of a mammalian reproductive study to derive the RfD based on the NOAEL (12.5 mg/kg-day ÷ 1000). USEPA assigned a confidence level of "Low" to the RfD. USEPA has not determined a cancer classification for fluometuron (USEPA, 2023a). Therefore, a cancer slope factor was not derived. The IRIS file for fluometuron is provided in **Attachment B**.

A drinking water lifetime health advisory level (HAL) of 0.09 milligrams per Liter (mg/L) is available from the USEPA (2018). The HAL is based on the RfD of 0.013 mg/kg-day established in IRIS and assumes daily exposure to fluometuron in drinking water for a lifetime. USEPA has not established an MCL or a secondary drinking water standard (USEPA, 2023b). No odor or taste thresholds have been established.

3. Derivation of Risk-Based GWQS

A systemic threshold concentration for fluometuron was derived in accordance with 15A NCAC 02L.0202(c)(1) as follows:

Derivation of Noncancer Systemic Threshold Concentration for Fluometuron			
Parameter	**Value**	**Units**	**Notes/Source**
Oral Reference Dose (RfD)	0.013	mg/kg-day	IRIS (USEPA, 2023a)
Body Weight (WT)	70	kg	NCAC 02L.0202 (c)(1)
Relative Source Contribution (RSC)	0.2	unitless	NCAC 02L.0202 (c)(1). Value for organics
Water Ingestion Rate (WI)	2	L/day	NCAC 02L.0202 (c)(1)
Conversion Factor (CF)	1000	µg/mg	NCAC 02L.0202 (c)(1)
Noncancer Systemic Threshold Concentration	0.09	mg/L	[(RfD x WT x RSC)/WI] x CF

There is no cancer slope factor for fluometuron and a GWQS for the cancer endpoint is not calculated.

4. Recommended IMAC

The table below summarizes the available thresholds for fluometuron.

Selection of Proposed IMAC for Fluometuron			
Parameter	**Value**	**Units**	**Notes/Source**
Noncancer Systemic Threshold Concentration	0.09	mg/L	Calculated above
Concentration corresponding to Cancer Risk 10^{-6}	--	--	Not carcinogenic
Taste Threshold Value	--	--	No threshold identified
Odor Threshold Value	--	--	Odorless; no threshold identified
Maximum Contaminant Level (MCL)	--	--	USEPA (2023b)
National Secondary Drinking Water Standard	--	--	USEPA (2023b)
Lifetime Health Advisory Level (HAL)	0.09	mg/L	USEPA (2018)
Proposed Interim Maximum Allowable Concentration (IMAC)	0.09	mg/L	Lowest value selected; USEPA HAL and calculated noncancer threshold concentration.

Based on the review and calculations provided here, an IMAC of 0.09 mg/L is proposed for fluometuron, based on USEPA's lifetime HAL and the calculated noncancer systemic threshold concentration.

5. References

NCDEQ. 2022. North Carolina Department of Environmental Quality, Division of Water Resources Standard Operating Procedure for Establishing Interim Maximum Allowable Concentrations (IMACs) per 15A NCAC 02L .0202 (c). Revised April.

PubChem. 2023. Fluometuron Compound Summary. https://pubchem.ncbi.nlm.nih.gov/compound/16562. Accessed June 2023.

USEPA. 2018. 2018 Edition of the Drinking Water Standards and Health Advisories Tables. EPA 822-F-18-001. Office of Water. USEPA. March.

USEPA. 2023a. Integrated Risk Information System (IRIS) database [online]. Environmental Criteria and Assessment Office, US Environmental Protection Agency, Washington, DC. https://www.epa.gov/iris. Accessed June 2023.

USEPA. 2023b. National Primary Drinking Water Regulations and Secondary Drinking Water Regulations. https://www.epa.gov/sdwa. Accessed June 2023.

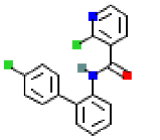
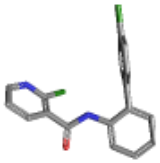
Attachment A

PubChem File

PubChem

COMPOUND SUMMARY

Boscalid

PubChem CID	213013
Structure	 2D  3D Find Similar Structures
Chemical Safety	 Environmental Hazard Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula	$C_{18}H_{12}Cl_2N_2O$
Synonyms	Boscalid 188425-85-6 Nicobifen Endura Emerald More...
Molecular Weight	343.2
Dates	Modify 2023-05-05 Create 2005-08-09

Boscalid is a pyridinecarboxamide obtained by formal condensation of the carboxy group of 2-chloronicotinic acid with the amino group of 4'-chlorobiphenyl-2-amine. A fungicide active against a broad range of fungal pathogens including Botrytis spp., Alternaria spp. and Sclerotinia spp. for use on a wide range of crops including fruit, vegetables and ornamentals. It has a role as an EC 1.3.5.1 [succinate dehydrogenase (quinone)] inhibitor, an environmental contaminant, a xenobiotic and an antifungal agrochemical. It is a member of biphenyls, a pyridinecarboxamide, a member of monochlorobenzenes and an anilide fungicide. It is functionally related to a nicotinic acid.

▸ ChEBI

Boscalid is a fungicide developed by BASF and launched in 2003 for use on food crops. It works as a **succinate** dehydrogenase inhibitor to kill fungal target organisms. It is practically nontoxic to terrestrial animals and is moderately toxic to aquatic animals on an acute exposure basis. In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased body weights and body weight gains (primarily in mice) and effects on the liver (increase in weights, changes in enzyme levels and histopathological changes) as well as on the thyroid (increase in weights and histopathological changes). In a developmental toxicity study in rats, no developmental toxicity was observed in the fetuses at the highest dose tested. Boscalid is classified as, suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential, according to the EPA.

- **Toxin and Toxin Target Database (T3DB)**

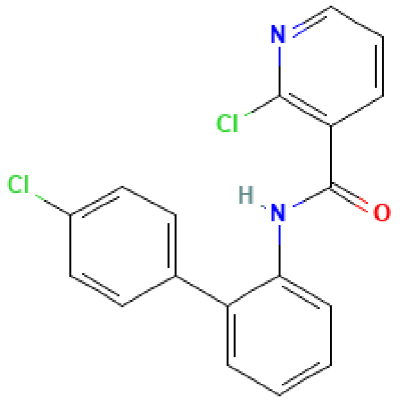
Boscalid has been investigated for the treatment of OSDI, Glaucoma, Staining, Schirmers, and Disease Severity, among others.

- **DrugBank**

1 Structures

1.1 2D Structure

Chemical Structure Depiction



PubChem

1.2 3D Conformer

PubChem

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

2-chloro-*N*-[2-(4-chlorophenyl)phenyl]pyridine-3-carboxamide

Computed by Lexichem TK 2.7.0 (PubChem release 2021.05.07)

PubChem

2.1.2 InChI

InChI=1S/C18H12Cl2N2O/c19-13-9-7-12(8-10-13)14-4-1-2-6-16(14)22-18(23)15-5-3-11-21-17(15)20/h1-11H,(H,22,23)

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.3 InChIKey

WYEMLYFITZORAB-UHFFFAOYSA-N

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.4 Canonical SMILES

C1=CC=C(C(=C1)C2=CC=C(C=C2)Cl)NC(=O)C3=C(N=CC=C3)Cl

Computed by OEChem 2.3.0 (PubChem release 2021.05.07)

PubChem

2.2 Molecular Formula

C18H12Cl2N2O

Wikipedia; PubChem

2.3 Other Identifiers

2.3.1 CAS

188425-85-6

- CAS Common Chemistry; ChemIDplus; DrugBank; EPA DSSTox; European Chemicals Agency (ECHA); FDA Global Substance Registration System (GSRS); Hazardous Substances Data Bank (HSDB)

2.3.2 European Community (EC) Number

606-143-0

- European Chemicals Agency (ECHA)

2.3.3 UNII

32MS8ZRD1V

- FDA Global Substance Registration System (GSRS)

2.3.4 DSSTox Substance ID

DTXSID6034392

- EPA DSSTox

2.3.5 Nikkaji Number

J1.989.940C

- Japan Chemical Substance Dictionary (Nikkaji)

2.3.6 Wikipedia

Boscalid

- Wikipedia

Emerald

- Wikipedia

2.3.7 Wikidata

Q894358

Wikidata

2.3.8 Metabolomics Workbench ID

153713

Metabolomics Workbench

2.4 Synonyms

2.4.1 MeSH Entry Terms

2-chloro-N-(4-chlorobiphenyl-2-yl)nicotinamide
boscalid

Medical Subject Headings (MeSH)

2.4.2 Depositor-Supplied Synonyms

Boscalid	32MS8ZRD1V	2-CHLORO-N-(4'-CHLORO(1,1'-BIPHENYL)-2-YL)-3-PYRIDINECARBOXAMIDE
188425-85-6	DTXSID6034392	3-Pyridinecarboxamide, 2-chloro-N-(4'-chloro(1,1'-biphenyl)-2-yl)-
Nicobifen	BAS 510 F	HSDB 7499
Endura	CHEBI:81822	BOSCALID [HSDB]
Emerald	NCGC00163735-04	EMERALD [INCI]
2-Chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide	Anilide	BOSCALID [MI]
Boscalid [ISO]	Cantus	SCHEMBL18517
2-chloro-N-(4'-chlorobiphenyl-2-yl)nicotinamide	C18H12Cl2N2O	CHEMBL1076544
2-chloro-N-[2-(4-chlorophenyl)phenyl]pyridine-3-carboxamide	2-chloro-N-{4'-chloro-[1,1'-biphenyl]-2-yl}pyridine-3-carboxamide	DTXCID4014392
3-Pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)-	BAS 510F	AMY22452
Bas 510	UNII-32MS8ZRD1V	ZINC3612929
Bas-510	2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide	Tox21_400045

PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	343.2	Computed by PubChem 2.1 (PubChem release 2021.05.07)
XLogP3-AA	4.9	Computed by XLogP3 3.0 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	1	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Rotatable Bond Count	3	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Exact Mass	342.0326684	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Monoisotopic Mass	342.0326684	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	42 Å^2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Heavy Atom Count	23	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	399	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.05.07)

PubChem

3.2 Experimental Properties

3.2.1 Physical Description

White solid; [Merck Index] White powder; [MSDSonline]

Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

3.2.2 Color/Form

White crystalline

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.3 Odor

Odorless

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.4 Melting Point

142.8 to 143.8 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.5 Solubility

In water, 4.6 mg/L at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

Solubility in n-heptane, <10 g/L, 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

Solubility in acetone, 16-20 g/100 mL; acetonitrile, 4-5 g/100 mL; methanol, 4-5 g/100 mL; ethylacetate, 6.7-9 g/100mL; dichloromethane, 20-25 g/100 mL; toluene, 2-2.5 g/100 mL; 1-octanol, <1 g/100 mL, all at 20 °C

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.6 Density

1.381 at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.7 Vapor Pressure

0.00000001 [mmHg]

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

7.2X10-4 mPa /5.4X10-10 mm Hg/ at 20 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.8 LogP

log Kow = 2.96

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.9 Henry's Law Constant

Henry's Law constant = 5.178X10-5 Pa- cu m/mol /5.3X10-11 atm-cu m/mol/ at 25 °C

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

3.2.10 Stability/Shelf Life

Stable under recommended storage conditions.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ Hazardous Substances Data Bank (HSDB)

3.2.11 pH

pH = 5.5 at 23 °C (1% solution)

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

▸ Hazardous Substances Data Bank (HSDB)

3.2.12 Ionization Efficiency

Ionization mode	Positive
logIE	2.55
pH	2.7
Instrument	Agilent XCT

Ion source	Electrospray ionization
Additive	formic acid (5.3nM)
Organic modifier	MeCN (80%)
Reference	DOI:10.1038/s41598-020-62573-z

Kruve Lab, Ionization & Mass Spectrometry, Stockholm University

3.2.13 Dissociation Constants

Does not dissociate

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

3.2.14 Collision Cross Section

171.67 Å^2 [M+H]$^+$ [CCS Type: TW]

https://pubs.acs.org/doi/abs/10.1021/acs.analchem.7b00741

CCSbase

178.57 Å^2 [M-H]$^-$

175.28 Å^2 [M+H]$^+$

179.04 Å^2 [M+Na]$^+$

S61 | UJICCSLIB | Collision Cross Section (CCS) Library from UJI | DOI:10.5281/zenodo.3549476

NORMAN Suspect List Exchange

3.2.15 Other Experimental Properties

White powder; faintly smoky odor; mp: 143.3 to 143.6 °C; density: 1.394 g/cu cm /Technical grade/

USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

Stable to hydrolysis at pH 4, 5, 7 and 9; stable to aqueous photolysis

MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)

Hazardous Substances Data Bank (HSDB)

3.2.16 Chemical Classes

Pesticides -> Fungicides

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

4 Spectral Information

4.1 Mass Spectrometry

4.1.1 GC-MS

Showing 2 of 3 View More

NIST Number	366503
Library	Main library
Total Peaks	166
m/z Top Peak	140
m/z 2nd Highest	112
m/z 3rd Highest	142
Thumbnail	

NIST Mass Spectrometry Data Center

Source of Spectrum	Prof. L. Mondello (Chromaleont s.r.l./Univ. Messina, Italy)
Source of Sample	Sigma-Aldrich Cat. #33875
Copyright	Copyright © 2016-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

4.1.2 MS-MS

Showing 2 of 6 View More

Spectra ID	2226978
Ionization Mode	Positive
SPLASH	splash10-00di-0090000000-cc17078aea1a98911337
Top 5 Peaks	271.0862 100 272.0933 84.48 243.0908 26.13 254.0823 16.82 139.9887 15.92
Thumbnail	

Human Metabolome Database (HMDB)

Spectra ID	2231680
Ionization Mode	Positive
SPLASH	splash10-0006-0049000000-8426425d727d94705a43
Top 5 Peaks	341.0229 100 228.0225 78.38 343.0244 62.96
Thumbnail	

Human Metabolome Database (HMDB)

4.1.3 LC-MS

Showing 2 of 46 View More

Accession ID	MSBNK-Athens_Univ-AU232601
Authors	Nikiforos Alygizakis, Katerina Galani, Nikolaos Thomaidis, University of Athens
Instrument	Bruker maXis Impact
Instrument Type	LC-ESI-QTOF
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	10 eV
Fragmentation Mode	CID

Column Name	Acclaim RSLC C18 2.2um, 2.1x100mm, Thermo
Retention Time	9.441 min
Precursor m/z	343.0399
Precursor Adduct	[M+H]+
Top 5 Peaks	343.04 999 345.0367 506 344.0432 155 307.0627 42 139.9887 35
SPLASH	splash10-0006-0009000000-591e6e2226a81639a618
Thumbnail	
License	CC BY

MassBank Europe

Accession ID	MSBNK-Athens_Univ-AU232602
Authors	Nikiforos Alygizakis, Katerina Galani, Nikolaos Thomaidis, University of Athens
Instrument	Bruker maXis Impact
Instrument Type	LC-ESI-QTOF
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	20 eV
Fragmentation Mode	CID

Column Name	Acclaim RSLC C18 2.2um, 2.1x100mm, Thermo
Retention Time	9.463 min
Precursor m/z	343.0399
Precursor Adduct	[M+H]+
Top 5 Peaks	307.0632 999 343.04 545 345.0364 323 139.9886 313 309.0603 201
SPLASH	splash10-0a4i-0109000000-0ecd56268ec733edc02c
Thumbnail	
License	CC BY

MassBank Europe

4.1.4 Other MS

Showing 2 of 3 View More

MoNA ID	CCMSLIB00001058945
MS Category	Experimental
MS Type	Other
MS Level	MS2
Precursor Type	[M+H]+
Precursor m/z	369.217

Instrument	Maxis HD qTOF
Ionization Mode	positive
Top 5 Peaks	149.060333 100 133.066055 39.95 119.060516 13.07 91.054398 10.56 105.070152 9.59
SPLASH	splash10-0002-0900000000-e7af1cb312c23ffb73fb
Thumbnail	

MassBank of North America (MoNA)

MoNA ID	CCMSLIB00001058753
MS Category	Experimental
MS Type	Other
MS Level	MS2
Precursor Type	[M+Na]+
Precursor m/z	391.199
Instrument	Q-Exactive Plus Orbitrap Res 14k
Ionization Mode	positive
Top 5 Peaks	241.130539 100 72.081207 75.30 219.149689 28.13 391.201233 17.69

	335.138245 12.67
SPLASH	splash10-006x-5192000000-1b8f299a4832762a05a6
Thumbnail	

▸ MassBank of North America (MoNA)

5 Related Records

5.1 Related Compounds with Annotation

PubChem

5.2 Related Compounds

Same Connectivity	6 Records
Same Parent, Connectivity	14 Records
Same Parent, Exact	9 Records
Mixtures, Components, and Neutralized Forms	56 Records
Similar Compounds	411 Records
Similar Conformers	1,938 Records

PubChem

5.3 Substances

5.3.1 Related Substances

All	196 Records
Same	125 Records

Mixture	71 Records

PubChem

5.3.2 Substances by Category

PubChem

5.4 Entrez Crosslinks

PubMed	45 Records
Taxonomy	4 Records
Gene	352 Records

PubChem

5.5 NCBI LinkOut

NCBI

6 Chemical Vendors

PubChem

7 Drug and Medication Information

7.1 FDA National Drug Code Directory

- National Drug Code (NDC) Directory

BOSCALID is an active ingredient in the product EMERALD.

- National Drug Code (NDC) Directory

7.2 Clinical Trials

7.2.1 ClinicalTrials.gov

- ClinicalTrials.gov

8 Agrochemical Information

8.1 Agrochemical Category

Fungicide

- EPA Pesticide Ecotoxicity Database

Pesticide active substances

- EU Pesticides Database

Fungicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | ***DOI:10.5281/zenodo.3862688***

- NORMAN Suspect List Exchange

8.2 Agrochemical Transformations

Boscalid has known environmental transformation products that include M510M47, M510F49, Boscalid metabolite 1, M510F08, and M510F50.

S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 | ***DOI:10.5281/zenodo.3544759***

- NORMAN Suspect List Exchange

8.3 EU Pesticides Data

Active Substance	boscalid (formerly nicobifen)
Status	Date of Approval: 01/08/2008 Expiration of Approval: 31/07/2023 [Reg. (EC) No 1107/2009]
Legislation	Reg. (EU) 2022/708, 08/44/EC, Reg. (EU) 2018/917, Reg. (EU) 2019/707, Reg. (EU) 2020/869, Reg. (EU) 2021/745, Reg. (EU) No 540/2011
ADI	0.04 mg/kg bw/day [08/44/EC]
AOEL	0.1 mg/kg bw/day [08/44/EC]

- EU Pesticides Database

8.4 USDA Pesticide Data Program

Pesticide	Boscalid
Apple Juice	EPA tolerance level: 3.0 [ppm]
Blueberries, Cultivated,	EPA tolerance level: 13.0 [ppm]
Bananas	EPA tolerance level: 0.40 [ppm] (Import Tolerance)
Broccoli	EPA tolerance level: 6.0 [ppm]

Blueberries, Frozen	EPA tolerance level: 13.0 [ppm]
Cauliflower	EPA tolerance level: 6.0 [ppm]
Cantaloupe	EPA tolerance level: 3.0 [ppm]
Carrots	EPA tolerance level: 2.0 [ppm]
Eggplant	EPA tolerance level: 3.0 [ppm]
Green Beans	EPA tolerance level: 5.0 [ppm]
Collard Greens	EPA tolerance level: 60 [ppm]
Kiwi Fruit	EPA tolerance level: NT
Orange Juice	EPA tolerance level: 2.0 [ppm]
Sweet Bell Peppers	EPA tolerance level: 3.0 [ppm]
Radishes	EPA tolerance level: 2.0 [ppm]
Summer Squash	EPA tolerance level: 3.0 [ppm]
Tangerines	EPA tolerance level: 2.0 [ppm]
Tomato Paste	EPA tolerance level: 3.0 [ppm]
Winter Squash	EPA tolerance level: 3.0 [ppm]

▸ USDA Pesticide Data Program

9 Minerals

Name	EMERALD

Athena Minerals

10 Pharmacology and Biochemistry

10.1 Absorption, Distribution and Excretion

Dermal Penetration (rat). Maximum % absorption: 0.01 mg/sq cm = 10.93 (24 hour exposure, 24 hour sacrifice) 0.10 mg/sq cm = 3.76 (24 hour exposure, 24 hour sacrifice) 1.00 mg/sq cm = 1.48 (10 hour exposure, 72 hour sacrifice /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.7 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

In the rat, Boscalid was readily absorbed and excreted following single oral 50 mg/kg; at single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion mainly by feces (80-98%). Biliary excretion 40- 50% of fecal activity at 50 mg/kg, 10% at 500 mg/kg. Urine, about 16% at 50 mg/kg, 3-5% at 500 mg/kg. Absorption about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns similar by gender or radiolabel position. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.7 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

10.2 Metabolism/Metabolites

Three ... groups of Wistar rats were treated and sampled ... for qualitative analyses of metabolites. ... Metabolites were separated by HPLC. Primary identification was by mass spectrometry (MS). ... The most important metabolites were **hydroxyl** or O-glucuronide metabolites on the diphenyl ring (usually para to the amide **nitrogen**), and S-glucuronide conjugation products displacing the **chlorine** on the **pyridine** ring of the parent compound. The **sulfur** originated from **glutathione** (**GSH**) addition to the ring. **GSH** was often cleaved to **cysteine** in bile or feces, or further degraded in feces to a **thiol**, which in turn was sometimes conjugated as a glucuronide). Tissue residues (liver, kidney, and plasma) were scant ... Some parent BAS 510 F was found in kidneys and plasma. Thus BAS 510 F was effectively metabolized and efficiently excreted.

California Environmental Protection Agency/Department of Pesticide Regulation; Summary of Toxicological Data for BAS 510 F, Chemical Code No.5790 p.9 (May 2, 2002, Revised May 20, 2013). Available from, as of June 15, 2016: ***https://www.cdpr.ca.gov/docs/risk/toxsums/toxsumlist.htm***

▸ **Hazardous Substances Data Bank (HSDB)**

/In the rat,/ metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with **glucuronic acid** or **sulfate**, or by conjugation of the parent with **glutathione** with cleavage to **sulfate** metabolites. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.7 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

10.3 Biological Half-Life

In the rat, the predominant route of excretion of BAS 510 F is fecal with urinary excretion being minor. The half-life of BAS 510 F is less than 24 hours.

BASF Submission to EPA; Request for consideration of a tolerances for residues of Boscalid (BAS 510F). EPA-HQ-OPP-2005-0145-004 (EPA Docket) (2005)

▸ **Hazardous Substances Data Bank (HSDB)**

10.4 Transformations

- NORMAN Suspect List Exchange

11 Use and Manufacturing

11.1 Uses

EPA CPDat Chemical and Product Categories

*The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products, Scientific Data, volume 5, Article number: 180125 (2018), **DOI:10.1038/sdata.2018.125***

▸ **EPA Chemical and Products Database (CPDat)**

Sources/Uses

Used as a broad spectrum carboxamide fungicide to control diseases in turf, field, row, orchard, and vineyard crops; [Merck Index]

Merck Index - O'Neil MJ, Heckelman PE, Dobbelaar PH, Roman KJ (eds). The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 15th Ed. Cambridge, UK: The Royal Society of Chemistry, 2013.

▸ **Haz-Map, Information on Hazardous Chemicals and Occupational Diseases**

Industrial Processes with risk of exposure

Farming (Pesticides) [Category: Industry]

▸ **Haz-Map, Information on Hazardous Chemicals and Occupational Diseases**

For boscalid (USEPA/OPP Pesticide Code: 128008) ACTIVE products with label matches. /SRP: Registered for use in the U.S. but approved pesticide uses may change periodically and so federal, state and local authorities must be consulted for currently approved uses./

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 21, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

▸ **Hazardous Substances Data Bank (HSDB)**

Fungicide, plant health product, seed treatment/protectant.

Crop Protection Handbook Volume 100, Meister Media Worldwide, Willoughby, OH 2014, p. 141

Hazardous Substances Data Bank (HSDB)

This is a man-made compound that is used as a pesticide.

Toxin and Toxin Target Database (T3DB)

11.1.1 Use Classification

Agrochemicals -> Pesticides

EU Pesticides Database

Fungicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | DOI:10.5281/zenodo.3862688

NORMAN Suspect List Exchange

Environmental transformation -> Pesticides (parent, predecessor)

S60 | SWISSPEST19 | Swiss Pesticides and Metabolites from Kiefer et al 2019 | DOI:10.5281/zenodo.3544759

NORMAN Suspect List Exchange

11.1.2 Household Products

Household & Commercial/Institutional Products

Information on 2 consumer products that contain Boscalid in the following categories is provided:

- Landscaping/Yard
- Pesticides

Consumer Product Information Database (CPID)

11.2 Methods of Manufacturing

Boscalid can be synthesized by reaction of 2-amino-4'-chlorobiphenyl in aqueous xylene with 2-chloro-3-pyridinecarbonyl chloride.

Muller F et al; Fungicides, Agricultural, 2. Individual Fungicides. Ullmann's Encyclopedia of Industrial Chemistry 7th ed. (1999-2016). NY, NY: John Wiley & Sons. Online Posting Date: October 15, 2011

Hazardous Substances Data Bank (HSDB)

2-Halopyridinecarboxamides of primary aromaticity in /the/ ortho-position-substituted monoamine, were prepared by reacting 2-halopyridinecarbonyl chloride with the corresponding aromatic monoamine in a solvent mixture containing water and greater than 1 solvent non-mixable with water; whereby the reaction mixture comprises a base in a quantity of 0-<10 mol% based on the 2-halopyridinecarbonyl chloride. Thus a mixture of water and 2-amino-4'-chlorobiphenyl in xylene was heated at 65 °C under stirring followed by /the/ addition of 2-chloro-3-pyridinecarbonyl chloride and stirring for 10 minutes at 95 °C to give 93% /boscalid/.

Mayer H et al; PCT Int Appl, WO 2003037868, BASF Aktiengesellschaft, Germany, 16pp. (2003)

Hazardous Substances Data Bank (HSDB)

Preparation: K. Eicken et al., European Patent Office patent 545099; eidem, United States of America patent 5589493 (1993, 1996 both to BASF).

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 237

Hazardous Substances Data Bank (HSDB)

11.3 Formulations/Preparations

Endura Fungicide (BASF Corporation): Active ingredient: Boscalid 70.0%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

Emerald Fungicide (BASF Corporation): Active ingredient: Boscalid 70.0%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

Boscalid Technical (BASF Corporation): Active ingredient: Boscalid 99.0%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

Pristine Fungicide (BASF Corporation): Active ingredient: Pyraclostrobin 12.8%; Boscalid 25.2%.

*National Pesticide Information Retrieval System's Database on Boscalid (188425-85-6). Available from, as of June 20, 2016: **https://npirspublic.ceris.purdue.edu/ppis/***

Hazardous Substances Data Bank (HSDB)

For more Formulations/Preparations (Complete) data for BOSCALID (14 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

11.4 General Manufacturing Information

The WHO Recommended Classification of Pesticides by Hazard identifies boscalid as unlikely to present an acute hazard in normal use; Main Use: fungicide, other than for seed treatment.

WHO International Programme on Chemical Safety; The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009 p.39 (2010)

Hazardous Substances Data Bank (HSDB)

12 Identification

12.1 Analytic Laboratory Methods

Sudden infant death syndrome (SIDS) and sudden intrauterine unexpected death syndrome (SIUDS) are an unresolved teaser in the social-medical and health setting of modern medicine and are the result of multifactorial interactions. Recently, prenatal exposure to environmental contaminants has been associated with negative pregnancy outcomes, and verification of their presence in fetal and newborn tissues is of crucial importance. A gas chromatography-tandem mass spectrometry (MS/MS) method, using a triple quadrupole analyzer, is proposed to assess the presence of 20 organochlorine pesticides, two organophosphate pesticides, one **carbamate** (boscalid), and a **phenol** (**bisphenol A**) in human brain tissues. Samples were collected during autopsies of infants and fetuses that died suddenly without any evident cause. The method involves a liquid-solid extraction using **n-hexane** as the extraction solvent. The extracts were purified with **Florisil** cartridges prior to the final determination. Recovery experiments using lamb brain spiked at three different concentrations in the range of 1-50 ng/g were performed, with recoveries ranging from 79 to 106%. Intraday and interday repeatability were evaluated, and relative standard deviations lower than 10% and 18%, respectively, were obtained. The selectivity and sensitivity achieved in multiple reaction monitoring mode allowed us to achieve quantification and confirmation in a real matrix at levels as low as 0.2-0.6 ng/g. Two MS/MS transitions were acquired for each analyte, using the Q/q ratio as the confirmatory parameter. This method was applied to the analysis of 14 cerebral cortex samples (ten SIUDS and four SIDS cases), and confirmed the presence of several selected compounds.

PMID:25665709

Termopoli V et al; Anal Bioanal Chem 407 (9): 2463-72 (2015)

Hazardous Substances Data Bank (HSDB)

Boscalid is a new-generation fungicide that has been detected in several bee matrices. The objective of this work was to characterize boscalid metabolites in honeybees based on in vivo experimentation, and next to verify the presence of these metabolites into honeybees from colonies presenting troubles. A methodology based on complementary mass spectrometric tools, namely ultra-high performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-QToF) or triple quadrupole mass spectrometry (UHPLC-QqQ) was implemented. Honeybees were sprayed with boscalid, at field rate (to induce the metabolization process) and the parent compound with its generated metabolites were then extracted using modified EU-QuEChERS method. The mass characteristics including exact mass, isotopic profile and mass fragments allowed assuming the structure of several metabolites. Some of them were unambiguously identified by comparison with synthesized analytical standards. The metabolites were resulted from hydroxylation and dechlorination of the parent compound as well as the substitution of a **chlorine** atom with a **hydroxyl** group. The metabolites were then quantified in bee samples collected from various beehives located in France.Boscalid and three of its metabolites were present in some samples at a level ranged between 0.2 and 36.3 ng/g.

PMID:27179242

Jabot C et al; Chemosphere 156: 245-51 (2016)

Hazardous Substances Data Bank (HSDB)

Analytical method. In plants the parent residue is extracted using an aqueous/organic solvent mixture followed by liquid/liquid partitioning and a column clean up. Quantitation is by gas chromatography using mass spectrometry (GC/MS). In livestock the residues are extracted with **methanol**. The extract is treated with enzymes in order to release the conjugated **glucuronic acid** metabolite. The residues are then isolated by liquid/liquid partition followed by column chromatography. The hydroxylated metabolite is acetylated followed by a column clean-up. The parent and acetylated metabolite are quantitated by gas chromatography with electron capture detection.

BASF Submission to EPA; Request for consideration of a tolerances for residues of Boscalid (BAS 510F). EPA-HQ-OPP-2005-0145-004 (EPA Docket) (2005)

Hazardous Substances Data Bank (HSDB)

13 Safety and Hazards

13.1 Hazards Identification

13.1.1 GHS Classification

Showing 1 of 2 View More

Pictogram(s)	 Environmental Hazard
GHS Hazard Statements	H411 (100%): Toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
Precautionary Statement Codes	P273, P391, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)
ECHA C&L Notifications Summary	*Aggregated GHS information provided by 288 companies from 3 notifications to the ECHA C&L Inventory.* *Reported as not meeting GHS hazard criteria by 3 of 288 companies. For more detailed information, please visit ECHA C&L website.* *Of the 2 notification(s) provided by 285 of 288 companies with hazard statement code(s).* *Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.*

▸ European Chemicals Agency (ECHA)

13.1.2 Hazard Classes and Categories

Aquatic Chronic 2 (100%)

▸ European Chemicals Agency (ECHA)

13.1.3 Hazards Summary

In high-dose animal studies, causes changes in thyroid and liver; [RTECS] Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential. Practically nontoxic to terrestrial animals and moderately toxic to aquatic animals for acute exposures; Ecological risks are low; Slowly degradable with low mobility in most soils; Exposure of aquatic animals is limited by chemical's tendency to sorb to sediments. [Reference #1]

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

13.1.4 Skin, Eye, and Respiratory Irritations

Not irritating in Primary Eye Irritation Test. Not irritating to skin in a Primary Dermal Irritation Test. /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.3 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

13.2 Fire Fighting

13.2.1 Fire Fighting Procedures

Suitable extinguishing media: Use **water** spray, alcohol-resistant foam, dry chemical or **carbon dioxide**.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Advice for firefighters: Wear self contained breathing apparatus for fire fighting if necessary.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.3 Accidental Release Measures

13.3.1 Cleanup Methods

ACCIDENTAL RELEASE MEASURES: Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Avoid breathing dust. Environmental precautions: Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided. Methods and materials for containment and cleaning up: Pick up and arrange disposal without creating dust. Sweep up and shovel. Keep in suitable, closed containers for disposal.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.3.2 Disposal Methods

SRP: Recycle any unused portion of the material for its approved use or return it to the manufacturer or supplier. Ultimate disposal of the chemical must consider: the material's impact on air quality; potential migration in air, soil or **water**; effects on animal, aquatic and plant life; and conformance with environmental and public health regulations. If it is possible or reasonable use an alternative chemical product with less inherent propensity for occupational harm/injury/toxicity or environmental contamination.

▸ **Hazardous Substances Data Bank (HSDB)**

Product: Offer surplus and non-recyclable solutions to a licensed disposal company. Contaminated packaging: Dispose of as unused product.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.3.3 Preventive Measures

Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Avoid dust formation. Avoid breathing vapors, mist or gas. Ensure adequate ventilation. Avoid breathing dust. Environmental precautions: Prevent further leakage or spillage if safe to do so. Do not let product enter drains. Discharge into the environment must be avoided.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Precautions for safe handling: Avoid contact with skin and eyes. Avoid formation of dust and aerosols. Provide appropriate exhaust ventilation at places where dust is formed.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Appropriate engineering controls: Handle in accordance with good industrial hygiene and safety practice. Wash hands before breaks and at the end of workday.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

SRP: Local exhaust ventilation should be applied wherever there is an incidence of point source emissions or dispersion of regulated contaminants in the work area. Ventilation control of the contaminant as close to its point of generation is both the most economical and safest method to minimize personnel exposure to airborne contaminants. Ensure that the local ventilation moves the contaminant away from the worker.

▸ **Hazardous Substances Data Bank (HSDB)**

13.4 Handling and Storage

13.4.1 Storage Conditions

Keep container tightly closed in a dry and well-ventilated place. Keep in a dry place.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

Safe Storage of Pesticides. Always store pesticides in their original containers, complete with labels that list ingredients, directions for use, and first aid steps in case of accidental poisoning. Never store pesticides in cabinets with or near food, animal feed, or medical supplies. Do not store pesticides in places where flooding is possible or in places where they might spill or leak into wells, drains, ground **water**, or surface **water**.

USEPA/Prevention, Pesticides, and Toxic Substances; Citizen's Guide to Pest Control and Pesticide Safety p.23 (September 1995) EPA 730-K-95-001

▸ **Hazardous Substances Data Bank (HSDB)**

13.5 Exposure Control and Personal Protection

13.5.1 Allowable Tolerances

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following raw agricultural commodities:

Commodity	Parts per million
Alfalfa, forage	30.0
Alfalfa, hay	65.0
Almond hulls	17
Apple, wet, pomace	10
Artichoke, globe	6.0
Avocado	1.5
Banana, import (No USA registration as of September 16, 2009)	0.40
Berry, low growing, subgroup 13-07G, except cranberry	4.5
Brassica, head and stem, subgroup 5A	3.0
Brassica, leafy greens, subgroup 5B	18.0
Bushberry subgroup 13-07B	13.0
Caneberry subgroup 13-07A	10.0
Canistel	1.5
Canola, refined oil	5.0
Citrus, dried pulp	4.5
Citrus, oil	85.0
Coffee, green bean, import (No USA registrations as of September 16, 2009)	0.05
Cotton, gin byproducts	55.0
Cucumber	0.5
Dill, seed	100
Endive, Belgium	6.0
Fruit, citrus, group 10-10	2.0
Fruit, pome, group 11-10	3.0
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	5.0
Fruit, stone, group 12-12	3.5
Grain, aspirated fractions	3.0
Grape, raisin	8.5
Herb subgroup 19A	150

Commodity	Parts per million
Hops, cones, dried	35
Leaf petioles subgroup 4B	45
Leafy greens subgroup 4A, except head lettuce and leaf lettuce	60
Lettuce, head	6.5
Lettuce, leaf	11.0
Mango	1.5
Nut, tree, group 14-12	0.70
Oilseed grup 20	3.5
Papaya	1.5
Pea and bean, dried shelled, except soybean, subgroup 6C, except cowpea, field pea and grain lupin	2.5
Pea and bean, succulent shelled, subgroup 6B, except cowpea	0.6
Peanut	0.05
Peanut, meal	0.15
Peanut, refined oil	0.15
Peppermint, tops	30.0
Persimmon	8.0
Sapodilla	1.5
Sapote, black	1.5
Sapote, mamey	1.5
Soybean, hulls	0.2
Soybean, seed	0.1
Soybean, vegetable	2.0
Spearmint, tops	30.0
Star apple	1.5
Turnip, greens	40.0
Vegegable, bulb, group 3-07	5.0
Vegetable, cucurbit, group 9, except cucumber	1.6
Vegetable, fruiting, group 8-10	3.0
Vegetable, legume, edible podded, subgroup 6A	1.6
Vegetable, root, subgroup 1A, except sugar beet, garden beet, radish, and turnip	1.0
Vegetable, tuberous and corm, subgroup 1C	0.05

40 CFR 180.589(a)(1); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), and metabolites 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide and glucuronic acid conjugate of 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide, calculated as the stoichiometric equivalent of boscalid in or on the following food commodities:

Commodity	Parts per million
Cattle, fat	0.30
Cattle, meat	0.10
Cattle, meat byproducts	0.35
Egg	0.02
Goat, fat	0.30
Goat, meat	0.10
Goat, meat byproducts	0.35
Hog, fat	0.20
Hog, meat	0.05
Hog, meat byproducts	0.10
Horse, fat	0.30
Horse, meat	0.10
Horse, meat byproducts	0.35
Milk	0.10
Poultry, fat	0.20
Poultry, meat	0.05
Poultry, meat byproducts	0.20
Sheep, fat	0.30
Sheep, meat	0.10
Sheep, meat byproducts	0.35

40 CFR 180.589(a)(2); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

Time-limited tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in connection with use of the pesticide under section 18 emergency exemptions granted by EPA. Compliance with the tolerance level specified below is to be determined by measuring only boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl). This tolerance will expire and is revoked on the date specified in the following table:

Commodity	Parts per million	Expiration/Revocation Date
Endive, Belgian	16	12/31/13

40 CFR 180.589(b); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

Tolerances are established for the indirect or inadvertent residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, 3-pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following commodities:

Commodity	Parts per million
Animal feed, nongrass, group 18, forage, except alfalfa	1.0
Animal feed, nongrass, group 18, hay, except alfalfa	2.0
Animal feed, nongrass, group 18, seed	0.05
Beet, garden, roots	0.1
Beet, sugar, roots	0.1
Cowpea, seed	0.1
Grain, cereal, forage, fodder and straw, group 16, forage	2.0
Grain, cereal, forage, fodder and straw, group 16, stover	1.5
Grain, cereal, forage, fodder and straw, group 16, straw	3.0
Grain, cereal, group 15	0.20
Grass, forage, fodder, and hay, group 17, forage	2.0
Grass, forage, fodder, and hay, group 17, hay	8.0
Grass, forage, fodder, and hay, group 17, seed screenings	0.20
Grass, forage, fodder, and hay, group 17, straw	0.30
Lupin, grain, grain	0.1
Pea,, field, seed	0.1
Radish, roots	0.1
Rice, hulls	0.50
Turnip, roots	0.1
Vegetable, foliage of legume, group 7, forage	1.5
Vegetable, foliage of legume, group 7, hay	2.0
Vegetable, foliage of legume, group 7, vines	0.05
Vegetable, leafy, except brassica, group 4, except celery, lettuce and spinach	1.0
Vegetable, leaves of root and tuber, group 2	0.1

*40 CFR 180.589(d); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: **https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

13.5.2 Personal Protective Equipment (PPE)

Eye/face protection: Safety glasses with side-shields conforming to EN166. Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

Skin protection: Handle with gloves.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

Body Protection: Impervious clothing. The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

Respiratory protection: For nuisance exposures use type P95 (US) or type P1 (EU EN 143) particle respirator. For higher level protection use type OV/AG/P99 (US) or type ABEK-P2 (EU EN 143) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

*Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: **https://www.sigmaaldrich.com/safety-center.html***

Hazardous Substances Data Bank (HSDB)

13.6 Regulatory Information

13.6.1 State Drinking Water Guidelines

(ME) MAINE 152.6 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

Hazardous Substances Data Bank (HSDB)

13.6.2 FIFRA Requirements

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following raw agricultural commodities:

Commodity
Alfalfa, forage
Alfalfa, hay
Almond hulls
Apple, wet, pomace
Artichoke, globe
Avocado
Banana, import (No USA registration as of September 16, 2009)
Berry, low growing, subgroup 13-07G, except cranberry
Brassica, head and stem, subgroup 5A

Commodity
Brassica, leafy greens, subgroup 5B
Bushberry subgroup 13-07B
Caneberry subgroup 13-07A
Canistel
Canola, refined oil
Citrus, dried pulp
Citrus, oil
Coffee, green bean, import (No USA registrations as of September 16, 2009)
Cotton, gin byproducts
Cucumber
Dill, seed
Endive, Belgium
Fruit, citrus, group 10-10
Fruit, pome, group 11-10
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F
Fruit, stone, group 12-12
Grain, aspirated fractions
Grape, raisin
Herb subgroup 19A
Hops, cones, dried
Leaf petioles subgroup 4B
Leafy greens subgroup 4A, except head lettuce and leaf lettuce
Lettuce, head
Lettuce, leaf
Mango
Nut, tree, group 14-12
Oilseed grup 20
Papaya
Pea and bean, dried shelled, except soybean, subgroup 6C, except cowpea, field pea and grain lupin
Pea and bean, succulent shelled, subgroup 6B, except cowpea
Peanut
Peanut, meal
Peanut, refined oil
Peppermint, tops

Commodity
Persimmon
Sapodilla
Sapote, black
Sapote, mamey
Soybean, hulls
Soybean, seed
Soybean, vegetable
Spearmint, tops
Star apple
Turnip, greens
Vegegable, bulb, group 3-07
Vegetable, cucurbit, group 9, except cucumber
Vegetable, fruiting, group 8-10
Vegetable, legume, edible podded, subgroup 6A
Vegetable, root, subgroup 1A, except sugar beet, garden beet, radish, and turnip
Vegetable, tuberous and corm, subgroup 1C

40 CFR 180.589(a)(1); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), and metabolites 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide and **glucuronic acid** conjugate of 2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide, calculated as the stoichiometric equivalent of boscalid in or on the following food commodities:

Commodity
Cattle, fat
Cattle, meat
Cattle, meat byproducts
Egg
Goat, fat
Goat, meat
Goat, meat byproducts
Hog, fat
Hog, meat
Hog, meat byproducts

Commodity
Horse, fat
Horse, meat
Horse, meat byproducts
Milk
Poultry, fat
Poultry, meat
Poultry, meat byproducts
Sheep, fat
Sheep, meat
Sheep, meat byproducts

40 CFR 180.589(a)(2); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Time-limited tolerances are established for residues of the fungicide boscalid, including its metabolites and degradates, in connection with use of the pesticide under section 18 emergency exemptions granted by EPA. Compliance with the tolerance level specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl). This tolerance will expire and is revoked on the date specified in the following table:

Commodity	Expiration/Revocation Date
Endive, Belgian	12/31/13

40 CFR 180.589(b); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Tolerances are established for the indirect or inadvertent residues of the fungicide boscalid, including its metabolites and degradates, in or on the commodities listed below. Compliance with the tolerance levels specified below is to be determined by measuring only boscalid, **3-pyridinecarboxamide**, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the following commodities:

Commodity
Animal feed, nongrass, group 18, forage, except alfalfa
Animal feed, nongrass, group 18, hay, except alfalfa
Animal feed, nongrass, group 18, seed
Beet, garden, roots
Beet, sugar, roots
Cowpea, seed
Grain, cereal, forage, fodder and straw, group 16, forage
Grain, cereal, forage, fodder and straw, group 16, stover
Grain, cereal, forage, fodder and straw, group 16, straw
Grain, cereal, group 15

Commodity
Grass, forage, fodder, and hay, group 17, forage
Grass, forage, fodder, and hay, group 17, hay
Grass, forage, fodder, and hay, group 17, seed screenings
Grass, forage, fodder, and hay, group 17, straw
Lupin, grain, grain
Pea,, field, seed
Radish, roots
Rice, hulls
Turnip, roots
Vegetable, foliage of legume, group 7, forage
Vegetable, foliage of legume, group 7, hay
Vegetable, foliage of legume, group 7, vines
Vegetable, leafy, except brassica, group 4, except celery, lettuce and spinach
Vegetable, leaves of root and tuber, group 2

40 CFR 180.589(d); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of June 14, 2016: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Pesticide Fact Sheet for Boscalid: Reason for Issuance: New Chemical; Date Issued: July 2003.

USEPA; Office of Prevention, Pesticides and Toxic Substances, Pesticide Fact Sheet for Boscalid p.1 (July 2003). Available from, as of October 4, 2016: ***https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-128008_01-Jul-03.pdf***

▸ **Hazardous Substances Data Bank (HSDB)**

13.7 Other Safety Information

13.7.1 Toxic Combustion Products

Special hazards arising from the substance or mixture: Carbon oxides, nitrogen oxides (NOx), **Hydrogen chloride** gas.

Sigma-Aldrich; Safety Data Sheet for Boscalid. Product Number: 33875, Version 4.4 (Revision Date 06/27/2014). Available from, as of June 13, 2016: ***https://www.sigmaaldrich.com/safety-center.html***

▸ **Hazardous Substances Data Bank (HSDB)**

13.7.2 Special Reports

USEPA; Office of Prevention, Pesticides and Toxic Substances, Pesticide Fact Sheet for Boscalid, Reason for Issuance: New Chemical (July 2003).[Available from, as of June 24, 2016: https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-128008_01-Jul-03.pdf]

- Hazardous Substances Data Bank (HSDB)

14 Toxicity

14.1 Toxicological Information

14.1.1 Toxicity Summary

IDENTIFICATION AND USE: Boscalid is a solid. It is used as fungicide, plant health product, seed treatment/protectant. HUMAN EXPOSURE AND TOXICITY: Boscalid may be genotoxic and cytotoxic in vitro in human peripheral blood lymphocytes. ANIMAL STUDIES: Boscalid has a low toxicity in animal studies. In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased body weights and body weight gains and effects on the liver (increase in weights, changes in enzyme levels and histopathological changes) as well as on the thyroid (increase in weights and histopathological changes). In a developmental toxicity study in rats, no developmental toxicity was observed in the fetuses at the highest dose tested. In a developmental toxicity study in rabbits, an increased incidence of abortions or early delivery was observed at the limit dose. The does and fetuses were equally sensitive to the test material. In a 2-generation reproduction study in rats, the NOAEL for parental toxicity was based on decreased body weight and body weight gain as well as hepatocyte degeneration. No reproductive toxicity was observed in this study at the highest dose tested. There was quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats, where decreases in pup body weights and body weight gains were seen in the absence of any maternal toxicity. In a two-year chronic toxicity study and a two-year carcinogenicity study in male and female rats, the combined data showed that, for thyroid follicular cell adenomas, males had a significant increasing trend, when compared with controls. There was no treatment-related increase in thyroid follicular cell carcinomas. The increase in thyroid follicular cell adenomas appeared to be treatment-related in males. Regarding females, combined data from the two rat studies indicated that there was an increasing trend for thyroid follicular cell adenomas. No carcinomas were observed in female. Boscalid was tested in five mutagenicity studies and was found to be negative in all of them. ECOTOXICITY STUDIES: Boscalid is categorized as practically nontoxic to birds in both an acute and subacute studies. Boscalid was harmless to adult Galendromus occidentalis. Boscalid use does not represent a risk to plants. Commercial producers of honey bee queens (Apis mellifera L.) have reported unexplained loss of immature queens during the larval or pupal stage. Many affected queen-rearing operations are situated among the almond orchards of California and report these losses in weeks after almond trees bloom. Almond flowers are a rich foraging resource for bees, but are often treated with fungicides, insecticides, and spray adjuvants during bloom. Anecdotal reports by queen producers associate problems in queen development with application of the fungicide Pristine (boscalid and **pyraclostrobin**). Chemical analysis revealed that low concentrations of **pyraclostrobin** (50 ppb), but no boscalid, were detectable in royal jelly secreted by nurse bees feeding on treated pollen.

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.2 Evidence for Carcinogenicity

Cancer Classification: Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential

USEPA Office of Pesticide Programs, Health Effects Division, Science Information Management Branch: "Chemicals Evaluated for Carcinogenic Potential" (April 2006)

▸ **Hazardous Substances Data Bank (HSDB)**

The EPA classified Boscalid (BAS 510 F) as, "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", and, therefore, the quantification of human cancer risk is not recommended. The cancer classification was based on the following weight of evidence considerations. First, in male Wistar rats, there was a significant trend (but not pair wise comparison) for the combined thyroid adenomas and carcinomas. This trend was driven by the increase in adenomas. Second, in the female rats, there was only a borderline significant trend for thyroid adenomas (there were no carcinomas)...

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.12 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.3 Carcinogen Classification

Carcinogen Classification	Not listed by IARC.

- Toxin and Toxin Target Database (T3DB)

14.1.4 Adverse Effects

Occupational hepatotoxin - Secondary hepatotoxins: the potential for toxic effect in the occupational setting is based on cases of poisoning by human ingestion or animal experimentation.

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

14.1.5 Toxicity Data

LC50 (rat) > 6,700 mg/m3

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

14.1.6 Antidote and Emergency Treatment

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing **water**. Do not induce vomiting. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

- Hazardous Substances Data Bank (HSDB)

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer **oxygen** by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with **water**. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of **water** for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160

- Hazardous Substances Data Bank (HSDB)

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag-valve-mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta agonist such as **albuterol** for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W TKO. Use 0.9% saline (NS) or lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with **diazepam** (**Valium**) or **lorazepam** (**Ativan**) ... . Use **proparacaine hydrochloride** to assist eye irrigation ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3rd revised edition, Elsevier Mosby, St. Louis, MO 2007, p. 160-61

- Hazardous Substances Data Bank (HSDB)

14.1.7 Human Toxicity Excerpts

/GENOTOXICITY/ The aim of this study was to investigate the genotoxic and cytotoxic potential of the Signum fungicide and its active ingredients (boscalid and **pyraclostrobin**) on human peripheral blood lymphocytes using the cytokinesis-block micronucleus (CBMN) assay. Micronuclei (MNi), nucleoplasmic bridges (NPBs), nuclear bud (NBUDs) formations, and the cytokinesis-block proliferation index (CBPI) were evaluated in treated lymphocytes in Go (cells were treated and then kept in culture without stimulation for 24 hr) and proliferation phases (cells were treated after 44 hr culture in medium containing phytohemagglutinin). MN formation in lymphocytes treated in G0 statistically increased at doses of 2, 6, and 25 ug/mL signum; 0.5 and 2 ug/mL boscalid; and 0.5, 1.5, and 2 ug/mL **pyraclostrobin**; while NPB formation increased at a dose of 0.25 ug/mL **pyraclostrobin**. All concentrations of each fungicide did not statistically increase NBUD formation, while the cytotoxicity increased the dependent on concentration in lymphocytes treated in G0 . Doses of 0.5, 1, 1.5, and 3 ug/mL signum; 0.5, 1, and 1.5 ug/mL boscalid; and 0.75 ug/mL **pyraclostrobin** statistically increased the MN formation in proliferating lymphocytes. NPB formation increased in proliferating lymphocytes at doses of 1, 1.5, 2, and 3 ug/mL signum and at a dose of 0.75 ug/mL **pyraclostrobin**. In addition, a dose of 0.75 ug/mL **pyraclostrobin** increased NBUD frequencies. Cytotoxicity increased with increasing concentrations of each fungicide. It is concluded that signum, boscalid, and **pyraclostrobin** may be genotoxic and cytotoxic in vitro human peripheral blood lymphocytes in consideration of each of the two protocols.

PMID:22730168

Cayir A et al; Environ Toxicol 29 (7): 723-32 (2014)

▸ **Hazardous Substances Data Bank (HSDB)**

/ALTERNATIVE and IN VITRO TESTS/ Nonpersistent pesticides are considered less harmful for the environment, but their impact as endocrine disruptors has not been fully explored. The pesticide Switch was applied to grape vines, and the maximum residue concentration of its active ingredients was quantified. The transactivation potential of the pesticides Acorit, Frupica, Steward, **Reldan**, Switch, Cantus, **Teldor**, and Scala and their active compounds (**hexythiazox**, **mepanipyrim**, **indoxacarb**, **chlorpyrifos-methyl**, **cyprodinil**, **fludioxonil**, boscalid, **fenhexamid**, and **pyrimethanil**) were tested on human estrogen receptor alpha (ERalpha), androgen receptor (AR) and arylhydrocarbon receptor (AhR) in vitro. Relative binding affinities of the pure pesticide constituents for AR and their effect on human breast cancer and prostate cancer cell lines were evaluated. Residue concentrations of Switch's ingredients were below maximum residue limits. **Fludioxonil** and **fenhexamid** were ERalpha agonists (EC50 -values of 3.7 and 9.0 uM, respectively) and had time-dependent effects on endogenous ERalpha-target gene expression (cyclin D1, **progesterone** receptor, and nuclear respiratory factor 1) in MCF-7 human breast cancer cells. **Fludioxonil**, **mepanipyrim**, **cyprodinil**, **pyrimethanil**, and **chlorpyrifos-methyl** were AhR-agonists (EC50 s of 0.42, 0.77, 1.4, 4.6, and 5.1 uM, respectively). Weak AR binding was shown for **chlorpyrifos-methyl**, **cyprodinil**, **fenhexamid**, and **fludioxonil**. Assuming a total uptake which does not take metabolism and clearance rates into account, our in vitro evidence suggests that pesticides could activate pathways affecting hormonal balance, even within permitted limits, thus potentially acting as endocrine disruptors.

PMID:23436777

Medjakovic S et al; Environ Toxicol 29 (10): 1201-16 (2014)

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.8 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 90-Day oral toxicity rodents (rats). NOAEL: 34/159 mg/kg/day (M/F); LOAEL: 137/395 mg/kg/day (M/F): M = increases in absolute and relative thyroid weights and increased incidence of thyroid hyperplasia as well as follicular epithelial hypertrophy; F = increases in absolute and relative thyroid weights. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 90-Day oral toxicity rodents (mice). NOAEL: 197/2209 mg/kg/day (M/F); LOAEL: 788/2209 mg/kg/day (M/F): M = increased liver weights and increased incidence of marked fatty change in the liver; F = not attained. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 90-Day oral toxicity in nonrodents (dogs). NOAEL: 7.6/8.1 mg/kg/day (M/F); LOAEL: 78.1/81.7 mg/kg/day (M/F): M = increased alkaline phosphatase activity and hepatic weights; F = increased alkaline phosphatase activity and hepatic weights. /From table/

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ 21/28-Day dermal toxicity (rats). NOAEL: 1000 mg/kg/day (Highest Dose Tested); LOAEL: >1000 mg/kg/day /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.5 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

For more Non-Human Toxicity Excerpts (Complete) data for BOSCALID (36 total), please visit the **HSDB record page**.

Hazardous Substances Data Bank (HSDB)

14.1.9 Non-Human Toxicity Values

LD50 Rat oral >5,000 mg/kg (Technical boscalid) /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.3 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

LD50 Rat dermal >2,000 mg/kg (Technical boscalid) /From table/

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.3 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

14.1.10 Ecotoxicity Values

EC50; Species: Danio rerio (Zebra Danio) age 6-8 hr postfertilization embryo; Conditions: freshwater, renewal, 26 °C; Concentration: 1.1337 uM for 120 hr; Effect: multiple effects: increased mortality, deformation; decreased hatch /formulation/

Padilla S et al; Reprod Toxicol 33 (2): 174-187 (2012) as cited in the ECOTOX database. Available from, as of July 13, 2016

Hazardous Substances Data Bank (HSDB)

14.1.11 Ecotoxicity Excerpts

/BIRDS and MAMMALS/ Risk to Avian Species (Acute/Chronic). Boscalid is categorized as practically nontoxic to birds in both an acute and subacute exposure basis, no acute levels of concern (LOC) are exceeded for birds feeding on any of the modeled food items (short grass, tall grass, broadleaf plants insects and seeds). However, chronic exposure to boscalid at the proposed application rate for strawberries, i.e., 5 applications of 0.350 lbs a.i./A with a 7-day reapplication interval, results in the chronic risk level of concern being exceeded for birds feeding on short grasses (RQ=1.08). Exposure to boscalid on other avian food items (tall grasses, broadleaf plants/insects, and seeds) at this application rate did not result in any exceedance of either acute or chronic LOCs. Based on maximum estimated concentrations on short grass the chronic risk LOC would be exceeded for approximately 4 days; however, if mean foliar residues were used to estimate exposure, chronic avian LOCs would not have been exceeded since mean foliar residues are roughly half maximum exposure values.

*USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.16 (July 2003). Available from, as of June 14, 2016: **https://www3.epa.gov/***

Hazardous Substances Data Bank (HSDB)

/AQUATIC SPECIES/ The presence of fungicides in the marine environment may pose risks to marine organisms, but little is known about fungicide effects on these organisms, especially invertebrates. The present study investigated the effects of the commonly used boscalid fungicide Filan on life history traits, feeding rate, and energy reserves (lipid, **glycogen**, and protein content)

of the marine amphipod Allorchestes compressa over 6 wk under laboratory conditions. Amphipods were exposed to 3 concentrations of Filan (1 ug, 10 ug, and 40 ug active ingredient [a.i.]/L), with 5 replicates per treatment. Lipid content and reproduction were the most sensitive measures of effect, with lipid content reduced by 53.8% at the highest concentration. Survival, growth, and other energy reserves of amphipods were also negatively affected by Filan, and the effects were concentration dependent. Antennal deformities were incidentally observed on the amphipods at a concentration of 40 ug a.i./L. The results of the present study indicate comprehensive effects of the boscalid fungicide Filan on A. compressa at environmentally relevant concentrations. The decline or absence of A. compressa in marine ecosystems could impair the ecosystem function because of their important role in trophic transfer and nutrient recycling. The authors' results suggest that even though the use of fungicides is often regarded as posing only a minor risk to aquatic organisms, the assessment of their long-term effects is critical.

PMID:26378894

Vu HT et al; Environ Toxicol Chem 35 (5): 1130-7 (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

/AQUATIC SPECIES/ Boscalid is moderately toxic to aquatic animals; however based on estimated exposure concentrations, the proposed uses of boscalid are not likely to represent a threat to either acute or chronic ecological risk to freshwater fish and invertebrates or to estuarine/marine fish at a maximum proposed multiple application rates as high as six applications of 0.350 lbs. a.i./A. However, the acute risk level of concern for endangered species is exceeded for estuarine/marine invertebrates. While boscalid is not expected to adversely affect aquatic animals whose lives are primarily spent in open **water**, bottom-dwelling (benthic) fauna may be more likely to encounter boscalid based on the chemical's persistence and tendency to sorb to sediments. Modeling of benthic exposure, based on a closed farm pond scenario over a 36-year period, did not exceed the chronic risk level of concern for sediment-dwelling animals.

USEPA; Office of Prevention, Pesticides and Toxic Substances; Pesticide Fact Sheet - Boscalid. p.16 (July 2003). Available from, as of June 14, 2016: ***https://www3.epa.gov/***

▸ **Hazardous Substances Data Bank (HSDB)**

/OTHER TERRESTRIAL SPECIES/ A laboratory evaluation of **fenbuconazole**, **myclobutanil propiconazole**, boscalid, **fenhexamid** and **pyraclostrobin** revealed these fungicides to be harmless to adult Galendromus occidentalis /mite/. None of these fungicides affected adversely fecundity and egg viability. Elemental **sulphur** also had no effect on adults and fecundity. However, 72.4% of the young larvae perished after hatching. The six novel fungicides are safer alternatives to **sulphur** in perennial crops in British Columbia.

PMID:18792796

Bostanian NJ et al; Exp Appl Acarol 47 (1): 63-9 (2009)

▸ **Hazardous Substances Data Bank (HSDB)**

For more Ecotoxicity Excerpts (Complete) data for BOSCALID (10 total), please visit the **HSDB record page**.

▸ **Hazardous Substances Data Bank (HSDB)**

14.1.12 Ongoing Test Status

EPA has released the Interactive Chemical Safety for Sustainability (iCSS) Dashboard. The iCSS Dashboard provides an interactive tool to explore rapid, automated (or in vitro high-throughput) chemical screening data generated by the Toxicity Forecaster (ToxCast) project and the federal Toxicity Testing in the 21st century (Tox21) collaboration. /The title compound was tested by ToxCast and/or Tox21 assays/[USEPA; ICSS Dashboard Application; Available from, as of July 7, 2016: http://actor.epa.gov/dashboard/]

▸ **Hazardous Substances Data Bank (HSDB)**

14.2 Ecological Information

14.2.1 EPA Ecotoxicity

Pesticide Ecotoxicity Data from EPA

EPA Pesticide Ecotoxicity Database

14.2.2 Environmental Fate/Exposure Summary

Boscalid's production may result in its release to the environment through various waste streams; its use as a fungicide will result in its direct release to the environment. If released to air, a vapor pressure of 5.4X10-10 mm Hg at 20 °C indicates boscalid will exist solely in the particulate phase in the atmosphere. Particulate-phase boscalid will be removed from the atmosphere by wet and dry deposition. Boscalid is stable to photolysis in **water** and, therefore, is not expected to be susceptible to direct photolysis by sunlight. If released to soil, boscalid is expected to be immobile based upon an estimated Koc of 9500. Volatilization from moist soil surfaces is not expected to be an important fate process based upon a Henry's Law constant of 5.11X10-11 atm-cu m/mole. Boscalid is not expected to volatilize from dry soil surfaces based upon its vapor pressure. Biodegradation half-lives in soil ranging from 96 to 578 days indicate that biodegradation is not an important environmental fate process in soil or **water**. If released into **water**, boscalid is expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from **water** surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 42 suggests the potential for bioconcentration in aquatic organisms is moderate. Boscalid is stable to hydrolysis. Occupational exposure to boscalid may occur through inhalation and dermal contact with this compound at workplaces where boscalid is produced or used. Monitoring data indicate that the general population may be exposed to boscalid via ingestion of some fruits and wines, dermal contact with spray in the vicinity of farms applying boscalid and contact with contaminated surface **water** or sediments in agricultural regions using this fungicide. (SRC)

Hazardous Substances Data Bank (HSDB)

14.2.3 Artificial Pollution Sources

Boscalid's production may result in its release to the environment through various waste streams; its use as a fungicide(1) will result in its direct release to the environment(SRC).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

14.2.4 Environmental Fate

TERRESTRIAL FATE: Based on a classification scheme(1), an estimated Koc value of 9500(SRC), determined from a structure estimation method(2), indicates that boscalid is expected to be immobile in soil(SRC). Volatilization of boscalid from moist soil surfaces is not expected to be an important fate process(SRC) given a Henry's Law constant of 5.11X10-11 atm-cu m/mole(3). Boscalid is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 5.4X10-10 mm Hg at 20 °C(3). Biodegradation half-lives in soil ranging from 96 to 578 days(4) indicate that biodegradation is not an important environmental fate process in soil(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

TERRESTRIAL FATE: Boscalid is generally persistent in the field based on terrestrial dissipation studies employing both cropped and bare plots in the US and Canada(1). The DT50 dissipation rate ranged from 27 to 372 days, generally being greater than 100 days(1).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

TERRESTRIAL FATE: The aim of this study was to analyze the environmental fate of the fungicide boscalid in a sandy soil. Boscalid was applied in spring 2010/11 to a cropland site in western Germany. Three years after second application 65 undisturbed soil samples were taken. Boscalid was extracted using accelerated solvent extraction (ASE). Boscalid contents in the plough horizon ranged between 0.12 and 0.53 with a field mean of 0.20 +/- 0.09 ug/kg. These contents were considerably lower compared to calculation using literature DT50 values, whereby a concentration of 16.89 ug kg/L was expected assuming a literature DT50 value of 345 days. Therefore, the measured field boscalid concentration only yields 1.2% of the expected value. To test whether the unknown extraction efficiency, losses from spray drift and interception can explain the mismatch between calculated and measured concentrations all these uncertainties were taken into account into calculations, but field concentrations and DT50 were still lower as expected. Leaching to deeper horizons was also studied but could not explain the discrepancy either. Moreover, a short-term incubation experiment using (14)C-labelled boscalid revealed also shorter DT50 values of 297-337 compared to the 345 days taken from literature. However, this DT50 value is still considerably larger compared to the 104-224 days that were calculated based on the field experiment. Our results indicate that boscalid dissipation under field conditions is much faster at agricultural sites with sandy soil type than expected from laboratory incubation experiments.

PMID:26688253

Karlsson AS et al; Chemosphere 14: 163-73 (2016)

Hazardous Substances Data Bank (HSDB)

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 9500(SRC), determined from a structure estimation method(2), indicates that boscalid is expected to adsorb to suspended solids and sediment(SRC). Volatilization from **water** surfaces is not expected(3) based upon a Henry's Law constant of 5.11X10-11 atm-cu m/mole(4). According to a classification scheme(5), an estimated BCF of 42(SRC), from its log Kow of 2.96(4) and a regression-derived equation(2), suggests the potential for bioconcentration in aquatic organisms is moderate(SRC). Biodegradation half-lives in soil ranging from 96 to 578 days(6) indicate that biodegradation is not an important environmental fate process in **water**(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

For more Environmental Fate (Complete) data for BOSCALID (6 total), please visit the **HSDB record page**.

Hazardous Substances Data Bank (HSDB)

14.2.5 Environmental Biodegradation

AEROBIC: A biodegradation half-life in soil ranging from 96 to 578 days and a dissipation half-life range of 27 to 372 days(1) indicate that boscalid is not expected to biodegrade rapidly under aerobic conditions(SRC).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

ANAEROBIC: Boscalid is stable in soil under anaerobic conditions(1).

(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub.

Hazardous Substances Data Bank (HSDB)

14.2.6 Environmental Abiotic Degradation

Boscalid is stable to hydrolysis at pH 5, 7 and 9 as indicated by no change to ring-labeled bocalid at a concentration of 3 mg active ingredient/L maintained in sterile aqueous buffer solutions for 30 days(1). Boscalid is stable to photolysis in **water**(2); 3 ug/L active ingredient remained unchanged following exposure to continuous irradiation using a **xenon** lamp for 15 days(1).

*(1) USEPA/OPPTS; Pesticide Fact Sheet: Boscalid. EPA Code 128008, July 2003. Washington, DC: Environmental Protection Agency, Off Prevent Pest Tox Sub. Available from, as of May 11, 2016: **https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1:** (2) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010)*

Hazardous Substances Data Bank (HSDB)

14.2.7 Environmental Bioconcentration

An estimated BCF of 42 was calculated in fish for boscalid(SRC), using a log Kow of 2.96(1) and a regression-derived equation(1). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is moderate(SRC). Accumulation is expected to be greatest in non-edible versus edible tissue and should depurate rapidly once organism is no longer exposed(4).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

14.2.8 Soil Adsorption/Mobility

The Koc of boscalid is estimated as 9500(SRC), using a log Kow of 2.96(1) and a regression-derived equation(2). According to a classification scheme(3), this estimated Koc value suggests that boscalid is expected to be immobile in soil(SRC). Boscalid is expected to sorb to aquatic sediments(4).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012.

Hazardous Substances Data Bank (HSDB)

Buffer zones such as ponds and ditches are used to reduce field-scale losses of pesticides from subsurface drainage waters to surface waters. The objective of this study was to assess the efficiency of these buffer zones, in particular constructed wetlands, focusing specifically on sorption processes. We modelled the sorption processes of three herbicides [**2-methyl-4-chlorophenoxyacetic acid** (**2,4-MCPA**), **isoproturon** and **napropamide**] and three fungicides (boscalid, **prochloraz** and **tebuconazole**) on four substrates (two soils, sediment and straw) commonly found in a pond and ditch in Lorraine (France). A wide range of Freundlich coefficient (K fads) values was obtained, from 0.74 to 442.63 mg(1 - n) L (n) kg(-1), and the corresponding K foc values ranged from 56 to 3,725 mg(1 - n) L (n) kg(-1). Based on potential retention, the substrates may be classified as straw >> sediments > soils. These results show the importance of organic **carbon** content and nature in the process of sorption. Similarly, the studied pesticides could be classified according to their adsorption capacity as follows: **prochloraz** >> **tebuconazole**-boscalid > **napropamide** >> **MCPA-isoproturon**. This classification is strongly influenced by the physico-chemical properties of pesticides, especially solubility and K oc. Straw exhibited the largest quantity of non-desorbable pesticide residues, from 12.1 to 224.2 mg/L for all pesticides. The presence of plants could increase soil-sediment sorption capacity. Thus, establishment and maintenance of plants and straw filters should be promoted to optimize sorption processes and the efficiency of ponds and ditches in reducing surface **water** pollution.

PMID:23784054
Vallee R et al; Environ Sci Pollut Res Int 21(7): 4895-905 (2014)

Hazardous Substances Data Bank (HSDB)

14.2.9 Volatilization from Water/Soil

The Henry's Law constant for boscalid is 5.11X10-11 atm-cu m/mole(1). This Henry's Law constant indicates that boscalid is expected to be essentially nonvolatile from water surfaces(2). Boscalid is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 5.4X10-10 mm Hg(1).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK: British Crop Protection Council. Boscalid (188425-85-6) (2008-2010) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990)

Hazardous Substances Data Bank (HSDB)

14.2.10 Environmental Water Concentrations

GROUNDWATER: Boscalid was not reported in groundwater samples taken from Italy in the regions of the Po River, Arno River, unspecified rivers in Tuscany, or the Fuscino Plain); research was conducted from 1997 through 2013(1).

PMID:24602913

(1) Meffe R, de Bustamante I; Sci Total Environ 481: 280-295 (2014)

Hazardous Substances Data Bank (HSDB)

SURFACE WATER: The US Geological Survey conducted a study of 33 fungicides and an additional 57 current-use pesticides applied to streams, ponds, and shallow groundwater located in areas of intense fungicide use within three geographic areas across the United States. Sampling sites were selected near or within farms using prophylactic fungicides at rates and types typical of their geographic location. Boscalid was detected in 72% of samples(1,2).

*(1) Reilly TJ et al; Chemosphere 89: 228-34 (2012). Available from, as of May 11, 2016: **https://www.ncbi.nlm.nih.gov/pubmed/?term=22564453** (2) USGS; Fungicides from Areas of Intense use Detected in Streams and Groundwater. Washington, DC: US Geol Survey. Environmental Health - Toxic Substances. Science Features. Available from, as of May 13, 2016: **https://toxics.usgs.gov/highlights/fungicide_occurrence.html***

Hazardous Substances Data Bank (HSDB)

SURFACE WATER: Boscalid was reported at a maximum concentration of 2,000 ng/L in an unspecified surface water sample taken from Italy (Po River, Arno River, unspecified rivers in Tuscany, or surface waters of the Fuscino Plain); research was conducted from 1997 through 2013(1).

PMID:24602913

(1) Meffe R, de Bustamante I; Sci Total Environ 481: 280-295 (2014)

Hazardous Substances Data Bank (HSDB)

14.2.11 Sediment/Soil Concentrations

SEDIMENT: The US Geological Survey conducted a study of 34 fungicides and an additional 57 current-use pesticides in bed sediments and suspended solids collected from areas of intense fungicide use within three geographic areas across the United States. Sampling sites were selected near or within agricultural research farms using prophylactic fungicides at rates and types typical of their geographic location. Boscalid was detected in 53% of sediments collected within highly agricultural areas(1,2).

*(1) Smalling KL et al; Sci Total Environ 447: 179-85 (2013). Available from, as of May 11, 2016: **https://www.ncbi.nlm.nih.gov/pubmed/23380566** (2) USGS; USGS; Fungicides from Areas of Intense use Detected in Streams and Groundwater. Washington, DC: US Geol Survey. Environmental Health - Toxic Substances. Science Features. Available from, as of May 13, 2016: **https://toxics.usgs.gov/highlights/fungicide_occurrence.html***

Hazardous Substances Data Bank (HSDB)

14.2.12 Food Survey Values

The effects of four fungicides commonly used for the control of fungal diseases in vines and grapes in the course of winemaking were tested. The concentration of fungicide residues was monitored throughout the process to establish their kinetics of dissipation. In all cases the percentages of dissipation were >68%, which shows the detoxificant effect of the winemaking process. On the other hand, the effect of the fungicide residues on the aroma composition of Tempranillo red wines was tested. To evaluate possible modifications on the aroma profile of wines, seven odorant series (ripe fruits, fresh fruits, lactic, floral, spicy, vinous, and herbaceous) were built from the odor activity values (OAVs) obtained for each volatile compound. Ripe fruits and fresh fruits were the major aromatic attributes in all Tempranillo red wines. These two odorant series registered the highest variations in their total OAVs with respect to the control wine, especially with the application of boscalid + **kresoxim-methyl** into vines, leading to a decrease in the ripe fruit and fresh fruit nuances of the resulting wines. Moreover, when the effect of these fungicides on the aroma of Tempranillo red wines was compared throughout two years (2012 and 2013), wines elaborated from grapes treated in the field with boscalid + **kresoxim-methyl** in 2013 displayed the highest variation in aroma profile with respect to control wine. During alcoholic fermentation, dissipation half-lives of 4.7 and 5.7 days in 2012 and 2013, respectively, were exhibited for boscalid + **kresoxim-methyl**(1).

PMID:26808836

(1) Boquerol-Paro R et al; J Agric Food Chem 64(6): 1344-54 (2016)

▸ Hazardous Substances Data Bank (HSDB)

Azoxystrobin, boscalid, **cyprodinil**, **fenhexamid**, and **pyrimethanil** are new generation fungicides extensively employed in order to combat diseases affecting vineyards worldwide. Owing to their physico-chemical characteristics, residues of these compounds on grapes are transferred to must and wine. In this study, a survey of the occurrence of these fungicides in international wines was carried out by using rapid antibody-based assays. Results are discussed as a function of wine type and sample geographical origin. 44.4% of the samples contained at least one of the targets (>10 ug/L). Fungicide residue occurrences were 22.4%, 19.2%, 18.8%, 6.8%, and 1.2% for **pyrimethanil**, boscalid, **fenhexamid**, **cyprodinil**, and **azoxystrobin**, respectively, while residue contents higher than 100 ug/L were found in 8.4% of the samples. This study shows that contamination of commercial wines with pesticides is an issue of worldwide relevance with potential implications for consumer health and international trade.

PMID:26593617

Esteve-Turrillas FA et al; Food Chem 196: 1279-86 (2016)

▸ Hazardous Substances Data Bank (HSDB)

Crops grown under plastic-clad structures or in greenhouses may be prone to an increased frequency of pesticide residue detections and higher concentrations of pesticides relative to equivalent crops grown in the open field. To test this we examined pesticide data for crops selected from the quarterly reports (2004-2009) of the UK's Pesticide Residue Committee. Five comparison crop pairs were identified whereby one crop of each pair was assumed to have been grown primarily under some form of physical protection ('protected') and the other grown primarily in open field conditions ('open'). For each pair, the number of detectable pesticide residues and the proportion of crop samples containing pesticides were statistically compared (n=100 samples for each crop). The mean concentrations of selected photolabile pesticides were also compared. For the crop pairings of cabbage ('open') vs. lettuce ('protected') and 'berries' ('open') vs. strawberries ('protected') there was a significantly higher number of pesticides and proportion of samples with multiple residues for the protected crops. Statistically higher concentrations of pesticides, including **cypermethrin**, **cyprodinil**, **fenhexamid**, boscalid and **iprodione** were also found in the protected crops compared to the open crops. The evidence here demonstrates that, in general, the protected crops possess a higher number of detectable pesticides compared to analogous crops grown in the open. This may be due to different pesticide-use regimes, but also due to slower rates of pesticide removal in protected systems. The findings of this study raise implications for pesticide management in protected-crop systems.

PMID:25465948

Allen G et al; Chemosphere 119: 1428-35 (2015)

▸ Hazardous Substances Data Bank (HSDB)

Greenhouse studies were conducted to evaluate the dissipation rate kinetics and estimate the behavior of selected pesticides after washing, peeling, simmering, and canning of tomato expressed as processing factor (PF). Two varieties (Marissa and Harzfeuer) were treated by six fungicides: **azoxystrobin**, boscalid, **chlorothalonil**, **cyprodinil**, **fludioxonil**, and **pyraclostrobin** at single and double dose and risk assessment defined as hazard quotient was performed. The QuEChERS method was used for sample preparation followed by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The dissipation of fungicides approximately fitted to a first-order kinetic model, with half-life values ranging from 2.49 and 2.67 days (**cyprodinil**) to 5.00 and 5.32 days (**chlorothalonil**) for Marissa and Harzfeuer variety, respectively. Results from processing studies showed that treatments have significant effects on the removal of the studied fungicides for both

varieties. The PFs were generally less than 1 (between 0.01 and 0.90) and did not depend on variety. The dietary exposure assessed based on initial deposits of application at single and double dose on tomatoes and concentration after each process with PF correction showed no concern to consumer health. Our results would be a useful tool for monitoring of fungicides in tomatoes and provide more understanding of residue behavior and risk posed by these fungicides.

PMID:26957431
Full text: ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4893063***
Jankowska M et al; Environ Sci Pollut Res Int Mar 9. (e-pub ahead of print) (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

14.2.13 Animal Concentrations

Boscalid is a new-generation fungicide that has been detected in several bee matrices. The objective of this work was to characterize boscalid metabolites in honeybees based on in vivo experimentation, and next to verify the presence of these metabolites into honeybees from colonies presenting troubles. A methodology based on complementary mass spectrometric tools, namely ultra-high performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-QToF) or triple quadrupole mass spectrometry (UHPLC-QqQ) was implemented. Honeybees were sprayed with boscalid, at field rate (to induce the metabolization process) and the parent compound with its generated metabolites were then extracted using modified EU-QuEChERS method. The mass characteristics including exact mass, isotopic profile and mass fragments allowed assuming the structure of several metabolites. Some of them were unambiguously identified by comparison with synthesized analytical standards. The metabolites were resulted from hydroxylation and dechlorination of the parent compound as well as the substitution of a **chlorine** atom with an **hydroxyl** group. The metabolites were then quantified in bee samples collected from various beehives located in France. Boscalid and three of its metabolites were present in some samples at a level ranged between 0.2 and 36.3 ng/g.

PMID:27179242
Jabot C et al; Chemosphere 156: 245-51 (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

There is considerable and ongoing debate as to the harm inflicted on bees by exposure to agricultural pesticides. In part, the lack of consensus reflects a shortage of information on field-realistic levels of exposure. Here, we quantify concentrations of neonicotinoid insecticides and fungicides in the pollen of oilseed rape, and in pollen of wildflowers growing near arable fields. We then compare this to concentrations of these pesticides found in pollen collected by honey bees and in pollen and adult bees sampled from bumble bee colonies placed on arable farms. We also compared this with levels found in bumble bee colonies placed in urban areas. Pollen of oilseed rape was heavily contaminated with a broad range of pesticides, as was the pollen of wildflowers growing nearby. Consequently, pollen collected by both bee species also contained a wide range of pesticides, notably including the fungicides **carbendazim**, boscalid, **flusilazole**, **metconazole**, **tebuconazole** and **trifloxystrobin** and the neonicotinoids **thiamethoxam**, **thiacloprid** and **imidacloprid**. In bumble bees, the fungicides **carbendazim**, boscalid, **tebuconazole**, **flusilazole** and **metconazole** were present at concentrations up to 73 nanogram/gram (ng/g). It is notable that pollen collected by bumble bees in rural areas contained high levels of the neonicotinoids **thiamethoxam** (mean 18 ng/g) and **thiacloprid** (mean 2.9 ng/g), along with a range of fungicides, some of which are known to act synergistically with neonicotinoids. Pesticide exposure of bumble bee colonies in urban areas was much lower than in rural areas. Understanding the effects of simultaneous exposure of bees to complex mixtures of pesticides remains a major challenge.

PMID:26760714
David A et al; Environ Int 88: 169-78 (2016)

▸ **Hazardous Substances Data Bank (HSDB)**

14.2.14 Probable Routes of Human Exposure

Occupational exposure to boscalid may occur through inhalation and dermal contact with this compound at workplaces where boscalid is produced or used. Monitoring data indicate that the general population may be exposed to boscalid via ingestion of some fruits and wines, dermal contact with spray in the vicinity of farms applying boscalid and contact with contaminated surface **water** or sediments in agricultural regions using this fungicide. (SRC)

▸ **Hazardous Substances Data Bank (HSDB)**

Concerns about pesticide drift from neighbouring vineyards affecting children attending school on a farm adjacent to an urban suburb of Cape Town, Western Cape in South Africa were investigated. The study involved a before-after design, measuring levels of environmental exposure before and during pesticide application activities on the neighbouring farms. Samples were collected in air, dust and grass cuttings at the preschool and primary school located on the farms during September-December in 2010 and tested for pesticides using multi-pesticide methods. Eleven different pesticides were detected in the various samples. Six of these chemicals (**endosulfan**, **dimethomorph**, **penconazole**, **cyprodinil**, boscalid and **bromopropylate**) were on the spraying schedules of the two farms neighbouring the schools and the timing and location of detection were generally consistent with farm application. Three pesticides detected (**chlorpyrifos**, **cypermethrin**, **permethrin**) are agents commonly used in household applications and one (**pyriproxifen**) is used in pet treatment agents. **Kresoxim-methyl**, the other pesticide detected, is likely to come from drift from other farms in the area. The concentration of pesticides was all lower than 0.1 ug/cu m in air and 0.1 ug/kg in dust and grass apart from **permethrin** and **cypermethrin**. The findings confirm the presence of drift onto the school premises and concentrations found in this study were generally low in comparison to that detected in other studies. Regular monitoring to track the effectiveness of containment and mitigation measures that reduce drift is recommended.

PMID:23995259

Dalvie MA et al; Sci Total Environ 1: 466-67 (2014)

Hazardous Substances Data Bank (HSDB)

15 Associated Disorders and Diseases

- Comparative Toxicogenomics Database (CTD)

- Therapeutic Target Database (TTD)

16 Literature

16.1 NLM Curated PubMed Citations

PubChem

16.2 Springer Nature References

- Springer Nature

16.3 Thieme References

- Thieme Chemistry

16.4 Wiley References

- Wiley

16.5 Depositor Provided PubMed Citations

- PubChem

16.6 Metabolite References

- Human Metabolome Database (HMDB)

16.7 Chemical Co-Occurrences in Literature

- PubChem

16.8 Chemical-Gene Co-Occurrences in Literature

PubChem

16.9 Chemical-Disease Co-Occurrences in Literature

PubChem

17 Patents

17.1 Depositor-Supplied Patent Identifiers

PubChem

Link to all deposited patent identifiers

PubChem

17.2 WIPO PATENTSCOPE

Patents are available for this chemical structure:

https://patentscope.wipo.int/search/en/result.jsf?inchikey=WYEMLYFITZORAB-UHFFFAOYSA-N

PATENTSCOPE (WIPO)

18 Interactions and Pathways

18.1 Chemical-Target Interactions

- Comparative Toxicogenomics Database (CTD); Toxin and Toxin Target Database (T3DB)

19 Biological Test Results

19.1 BioAssay Results

PubChem

20 Taxonomy

- KNApSAcK Species-Metabolite Database; LOTUS - the natural products occurrence database

21 Classification

21.1 MeSH Tree

Medical Subject Headings (MeSH)

21.2 ChEBI Ontology

ChEBI

21.3 KEGG: Pesticides

KEGG

21.4 ChemIDplus

- ChemIDplus

21.5 UN GHS Classification

- UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

21.6 EPA CPDat Classification

- EPA Chemical and Products Database (CPDat)

21.7 NORMAN Suspect List Exchange Classification

- NORMAN Suspect List Exchange

21.8 CCSBase Classification

- CCSbase

21.9 EPA DSSTox Classification

- EPA DSSTox

21.10 Consumer Product Information Database Classification

- Consumer Product Information Database (CPID)

21.11 LOTUS Tree

- LOTUS - the natural products occurrence database

21.12 FDA Drug Type and Pharmacologic Classification

National Drug Code (NDC) Directory

21.13 EPA Substance Registry Services Tree

EPA Substance Registry Services

22 Information Sources

FILTER BY SOURCE ALL SOURCES

1. **Athena Minerals**

   LICENSE

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   Emerald
   https://athena.unige.ch/cgi-bin/minfich.cgi?s=EMERALD

2. **CAS Common Chemistry**

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   Boscalid
   https://commonchemistry.cas.org/detail?cas_rn=188425-85-6

3. **ChemIDplus**

   LICENSE

   https://www.nlm.nih.gov/copyright.html

   Boscalid [ISO]
   https://pubchem.ncbi.nlm.nih.gov/substance/?source=chemidplus&sourceid=0188425856

   ChemIDplus Chemical Information Classification
   https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

4. **DrugBank**

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   Boscalid
   https://www.drugbank.ca/drugs/DB12792

5. **EPA DSSTox**

   LICENSE

   https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

   Boscalid
   https://comptox.epa.gov/dashboard/DTXSID6034392

   CompTox Chemicals Dashboard Chemical Lists
   https://comptox.epa.gov/dashboard/chemical-lists/

6. **European Chemicals Agency (ECHA)**

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3-Pyridinecarboxamide, 2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl)
https://echa.europa.eu/substance-information/-/substanceinfo/100.115.343

Boscalid (formerly Nicobifen)
https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/44859

7. FDA Global Substance Registration System (GSRS)

BOSCALID
https://gsrs.ncats.nih.gov/ginas/app/beta/substances/32MS8ZRD1V

8. Hazardous Substances Data Bank (HSDB)

BOSCALID
https://pubchem.ncbi.nlm.nih.gov/source/hsdb/7499

9. CCSbase

Boscalid

CCSbase Classification
https://ccsbase.net/

10. NORMAN Suspect List Exchange

Boscalid

NORMAN Suspect List Exchange Classification
https://www.norman-network.com/nds/SLE/

11. ChEBI

Boscalid
http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:81822

ChEBI Ontology
http://www.ebi.ac.uk/chebi/userManualForward.do#ChEBI%20Ontology

12. LOTUS - the natural products occurrence database

Boscalid
https://www.wikidata.org/wiki/Q894358

LOTUS Tree
https://lotus.naturalproducts.net/

13. ## Toxin and Toxin Target Database (T3DB)

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>
> http://www.t3db.ca/downloads

Boscalid
http://www.t3db.ca/toxins/T3D3800

14. ## ClinicalTrials.gov

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>
> https://clinicaltrials.gov/ct2/about-site/terms-conditions#Use

https://clinicaltrials.gov/

15. ## Comparative Toxicogenomics Database (CTD)

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>
> http://ctdbase.org/about/legal.jsp

2-chloro-N-(4-chlorobiphenyl-2-yl)nicotinamide
https://ctdbase.org/detail.go?type=chem&acc=C550088

16. ## Therapeutic Target Database (TTD)

Boscalid
https://idrblab.net/ttd/data/drug/details/D0R4EY

17. ## Consumer Product Information Database (CPID)

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>
> https://www.whatsinproducts.com/contents/view/1/6

Boscalid
https://www.whatsinproducts.com/chemicals/view/1/5008/188425-85-6

Consumer Products Category Classification
https://www.whatsinproducts.com/

18. ## EPA Chemical and Products Database (CPDat)

> LICENSE
>
> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

https://comptox.epa.gov/dashboard/DTXSID6034392#exposure

EPA CPDat Classification
https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

19. ## Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

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>
> https://haz-map.com/About

Boscalid
https://haz-map.com/Agents/3988

20. ## EPA Pesticide Ecotoxicity Database

> LICENSE
> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

https://ecotox.ipmcenters.org/

21. ## EU Pesticides Database

Boscalid (formerly nicobifen)
https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event=as.details&as_id=472

22. ## Human Metabolome Database (HMDB)

> LICENSE
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> http://www.hmdb.ca/citing

Boscalid
http://www.hmdb.ca/metabolites/HMDB0249353

HMDB0249353_msms_2226978
https://hmdb.ca/metabolites/HMDB0249353#spectra

23. ## Japan Chemical Substance Dictionary (Nikkaji)

http://jglobal.jst.go.jp/en/redirect?Nikkaji_No=J1.989.940C

24. ## KNApSAcK Species-Metabolite Database

Boscalid
http://www.knapsackfamily.com/knapsack_core/info.php?sname=C_ID&word=C00060571

25. ## Kruve Lab, Ionization & Mass Spectrometry, Stockholm University

boscalid

26. ## MassBank Europe

> LICENSE
> https://github.com/MassBank/MassBank-web/blob/main/MassBank-Project/LICENSE.txt

WYEMLYFITZORAB-UHFFFAOYSA-N
https://massbank.eu/MassBank/Result.jsp?inchikey=WYEMLYFITZORAB-UHFFFAOYSA-N

27. ## MassBank of North America (MoNA)

> LICENSE
> The content of the MoNA database is licensed under CC BY 4.0.
> https://mona.fiehnlab.ucdavis.edu/documentation/license

Boscalid
https://mona.fiehnlab.ucdavis.edu/spectra/browse?query=exists(compound.metaData.name:%27InChIKey%27%20and%20compound.metaData.value:%27WYEMLYFITZORAB-UHFFFAOYSA-N%27)

28. ## Metabolomics Workbench

Boscalid
https://www.metabolomicsworkbench.org/data/StructureData.php?RegNo=153713

29. ## National Drug Code (NDC) Directory

EMERALD
https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory

30. ## NIST Mass Spectrometry Data Center

BOSCALID
http://www.nist.gov/srd/nist1a.cfm

31. ## SpectraBase

Boscalid
https://spectrabase.com/spectrum/KCCDJ3TY9y0

Boscalid
https://spectrabase.com/spectrum/5QGEVjzhDBA

32. ## Springer Nature

https://pubchem.ncbi.nlm.nih.gov/substance/?source=15745&sourceid=23053073-915577709

33. ## Thieme Chemistry

https://pubchem.ncbi.nlm.nih.gov/substance/?source=22163&sourceid=23053073-915577709

34. ## USDA Pesticide Data Program

Boscalid
https://www.ams.usda.gov/datasets/pdp/pdpdata

35. ## Wikidata

boscalid
https://www.wikidata.org/wiki/Q894358

36. ## Wikipedia

boscalid
https://en.wikipedia.org/wiki/Succinate_dehydrogenase

Emerald
https://en.wikipedia.org/wiki/Emerald

37. ## Wiley

https://pubchem.ncbi.nlm.nih.gov/substance/?source=wiley&sourceid=67543

38. ## PubChem

https://pubchem.ncbi.nlm.nih.gov

39. ## Medical Subject Headings (MeSH)

2-chloro-N-(4-chlorobiphenyl-2-yl)nicotinamide
https://www.ncbi.nlm.nih.gov/mesh/67550088

MeSH Tree
http://www.nlm.nih.gov/mesh/meshhome.html

40. ## KEGG

Pesticides
http://www.genome.jp/kegg-bin/get_htext?br08007.keg

41. ## UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

GHS Classification Tree
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

42. ## EPA Substance Registry Services

EPA SRS List Classification
https://sor.epa.gov/sor_internet/registry/substreg/LandingPage.do

43. ## PATENTSCOPE (WIPO)

SID 389366395
https://pubchem.ncbi.nlm.nih.gov/substance/389366395

44. ## NCBI

https://www.ncbi.nlm.nih.gov/projects/linkout

Attachment B

IRIS File

Fluometuron; CASRN 2164-17-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Fluometuron

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Fluometuron
CASRN — 2164-17-2
Last Revised — 09/30/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
No adverse effects **103-Week Rat Feeding Study** **NCI, 1980**	NOAEL: 250 ppm diet (12.5 mg/kg/day) LEL: None	1000	1	1.3E-2 mg/kg/day

*Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

I.A.2. Principal and Supporting Studies (Oral RfD)

NCI (National Cancer Institute). 1980. Bioassay of Fluometuron for Possible Carcinogenicity, CAS No. 2164-17-2, NCI-CG-TR-195, NTP-80-11, NIH Publ. No. 80-1751. National Institute of Health, Bethesda, MD.

Groups of rats (50/sex/dose) were fed diets containing 0, 125, or 250 ppm of fluometuron for 103 weeks. All surviving animals were killed at 103 to 105 weeks. Mean body weights and survival of the dosed groups of male and female rats were essentially the same as those of the corresponding control group. No observed effects were seen at the highest dose tested, 250 ppm (12.5 mg/kg/day), which was the NOAEL for this study.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 1000 was used to account for the inter- and intraspecies differences and for the fact that the database on toxicity is incomplete (e.g., lacking a mammalian reproductive study). Furthermore, the available supporting studies are of low quality.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Data Considered for Establishing the RfD:

1) 103-Week Feeding - rat: Principal study - see previous description; no core grade

2) 90-Day Feeding - rat: NOEL=7.5 mg/kg/day; LEL=75 mg/kg/day (decrease in body weight and enlarged spleens); no core grade (Ciba Agrochemical, 1965a)

3) 90-Day Feeding - dog: NOEL=10 mg/kg/day; LEL=100 mg/kg/day (inflammatory reaction in kidney and liver); no core grade (Ciba Agrochemical, 1965b)

4) Teratology - rabbit: Maternal and Fetotoxic NOEL not established; LEL=50 mg/kg/day; minimum for teratogenicity otherwise supplementary (Ciba-Geigy, 1984)

5) 103-Week Feeding - mouse: NOEL=500 ppm (75 mg/kg/day); LEL=1000 ppm (150 mg/kg/day) (marginal increase in liver tumors); no core grade (NCI, 1980)

Data Gap(s): Chronic Rat Feeding Study; Chronic Dog Feeding Study; Rat Reproduction Study; Rat Teratology Study; Rabbit Teratology Study

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Low
RfD — Low

The principal study appears to be of low quality and is given a low confidence rating. Since the database on toxicity is incomplete and of apparently low quality, the database is given a low confidence rating. Low confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — Pesticide Registration Standard, 1985; Pesticide Registration Files

Agency Work Group Review — 07/08/1986, 03/18/1987

Verification Date — 03/18/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Fluometuron conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Fluometuron
CASRN — 2164-17-2

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Fluometuron
CASRN — 2164-17-2

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Fluometuron
CASRN — 2164-17-2

VI.A. Oral RfD References

Ciba Agrochemical Company. 1965a. MRID No. 00019034. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba Agrochemical Company. 1965b. MRID No. 00019035. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1984. MRID No. 00147554. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

NCI (National Cancer Institute). 1980. Bioassay of Fluometuron for Possible Carcinogenicity, CAS No. 2164-17-2, NCI-CG-TR-195, NTP-80-11, NIH Publ. No. 80-1751. National Institute of Health, Bethesda, MD.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Fluometuron
CASRN — 2164-17-2

Date	Section	Description
10/28/2003	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Fluometuron
CASRN — 2164-17-2
Last Revised — 09/30/1987

- 2164-17-2
- C 2059
- CIBA 2059
- COTORAN MULTI 50WP
- COTTONEX
- 1,1-DIMETHYL-3-(3-TRIFLUOROMETHYLPHENYL)UREA
- 1,1-DIMETHYL-3-(alpha,alpha,alpha-TRIFLUORO-m-TOLYL) UREA
- Fluometuron
- HERBICIDE C-2059
- LANEX
- NCI-C08695
- N-(3-TRIFLUOROMETHYLPHENYL)-N'-N'-DIMETHYLUREA
- N-(m-TRIFLUOROMETHYLPHENYL)-N',N'-DIMETHYLUREA
- PAKHTARAN
- 3-(5-TRIFLUORMETHYLPHENYL)-1,1-DIMETHYLHARNSTOFF
- 3-(m-TRIFLUOROMETHYLPHENYL)-1,1-DIMETHYLUREA
- UREA, 1,1-DIMETHYL-3-(alpha,alpha,alpha-TRIFLUORO-m-TOLYL)-
- UREA, N,N-DIMETHYL-N'-(3-(TRIFLUOROMETHYL)PHENYL)-

Derivation of Proposed Groundwater

Interim Maximum Allowable Concentration (IMAC)

Metolachlor

1. Introduction

North Carolina regulations [15A NCAC 02L.0202 (c)] allow a party to petition for the establishment of an Interim Maximum Allowable Concentration (IMAC) for a substance lacking a groundwater standard. In the absence of a groundwater standard for metolachlor, an IMAC is proposed in this document. The IMAC was developed in accordance with the North Carolina Department of Environmental Quality (NCDEQ) Division of Water Resources Standard Operating Procedure for Establishing IMACs (NCDEQ, 2022).

Per the regulations [15A NCAC 02L.0202 (c)], the groundwater quality standard (GWQS) is the lowest of the following:

1. Systemic threshold concentration;
2. Concentration corresponding to an incremental lifetime cancer risk of 10^{-6};
3. Taste threshold limit value;
4. Odor threshold limit value;
5. Maximum contaminant level (MCL);
6. National secondary drinking water standard.

The regulations [15A NCAC 02L.0202 (c)] state that the following sources, in order of preference, be used in establishing the above levels:

1. The United States Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS).
2. Health Advisories (USEPA Office of Drinking Water).
3. Other health risk assessment data published by USEPA.
4. Other relevant, published health risk assessment data, and scientifically valid peer-reviewed published toxicological data.

Section 2 provides an overview of metolachlor and a summary of available data. Risk-based GWQS are calculated in Section 3, and the proposed IMAC is presented in Section 4. References are provided in Section 5.

2. Metolachlor Data

Metolachlor (CAS No. 51218-45-2) is a registered herbicide used to control weeds in corn, soybean, and other crops. It is a tan to brown oily liquid and has a slightly sweet odor. The chemical structure and chemical properties are provided in **Attachment A** (PubChem, 2023).

An oral reference dose (RfD) of 0.15 milligrams per kilogram body weight per day (mg/kg-day) is available from IRIS (USEPA, 2023a) for metolachlor. The RfD, listed on IRIS in 1990, is based on two studies in

rats, including a two-year dietary study and a two-generation reproduction study. USEPA identified a no-observed effect level (NOEL) of 15 mg/kg-day in the dietary study, based on decreased body weight gain at a low effect level (LEL) of 150 mg/kg-day. A NOEL of 15 mg/kg-day was also identified in the reproductive study, based on an LEL of 50 mg/kg-day for reduced pup weight and reduced parental food consumption. USEPA applied uncertainty factors of 10 for extrapolation from laboratory animals to humans and 10 for uncertainty in the threshold for sensitive humans to derive the RfD based on the NOEL (15 mg/kg-day ÷ 100). USEPA assigned a confidence level of "High" to the RfD. USEPA classified metolachlor as a Class C, possible human carcinogen based on the appearance of proliferative liver lesions in the highest dose tested in female rats (USEPA, 2023a). However, a cancer slope factor was not derived. The IRIS file for metolachlor is provided in **Attachment B**.

A drinking water lifetime health advisory level (HAL) of 0.7 milligrams per Liter (mg/L) is available from the USEPA (2018). The HAL is based on an RfD of 0.1 mg/kg-day and assumes daily exposure to metolachlor in drinking water for a lifetime. The RfD of 0.1 mg/kg-day was derived by USEPA in 1995 based on a one-year feeding study in dogs. A NOEL of 9.7 mg/kg-day was established for decreased body weight gain, and an uncertainty factor of 100 was applied to derive the RfD (USEPA, 1995). USEPA has not established an MCL or a secondary drinking water standard (USEPA, 2023b). No odor or taste thresholds have been established.

It should be noted that metolachlor is currently undergoing registration review (Docket Number EPA-HQ-OPP-2014-0772). The Office of Chemical Safety and Pollution Prevention published a draft human health risk assessment on September 12, 2019 (USEPA, 2019). The 2019 risk assessment, provided in **Attachment C**, identified a no-observed adverse effect level (NOAEL) of 26 mg/kg-day based on the same two-generation reproductive study in rats used by USEPA to derive the 1990 IRIS RfD. After applying an uncertainty factor of 100 (extrapolation from animals to humans and intraspecies variation), USEPA derived an updated RfD of 0.26 mg/kg-day for metolachlor. USEPA also re-classified metolachlor as "not likely to be carcinogenic to humans" at doses that do not induce cellular proliferation in the liver, with risk quantified using a non-linear (RfD) approach.

3. Derivation of Risk-Based GWQS

A systemic threshold concentration for metolachlor was derived in accordance with 15A NCAC 02L.0202(c)(1) as follows:

Derivation of Noncancer Systemic Threshold Concentration for Metolachlor			
Parameter	**Value**	**Units**	**Notes/Source**
Oral Reference Dose (RfD)	0.15	mg/kg-day	IRIS (USEPA, 2023a)
Body Weight (WT)	70	kg	NCAC 02L.0202 (c)(1)
Relative Source Contribution (RSC)	0.2	unitless	NCAC 02L.0202 (c)(1). Value for organics
Water Ingestion Rate (WI)	2	L/day	NCAC 02L.0202 (c)(1)

Derivation of Noncancer Systemic Threshold Concentration for Metolachlor			
Parameter	**Value**	**Units**	**Notes/Source**
Conversion Factor (CF)	1000	µg/mg	NCAC 02L.0202 (c)(1)
Noncancer Systemic Threshold Concentration	1.05	mg/L	[(RfD x WT x RSC)/WI] x CF

Because the 2019 risk assessment is not final, the updated RfD was not used in the development of the proposed IMAC. However, use of the updated RfD would result in a higher GWQS of 1.82 mg/L.

There is no cancer slope factor for metolachlor and a GWQS for the cancer endpoint is not calculated.

4. Recommended IMAC

The table below summarizes the available thresholds for metolachlor.

Selection of Proposed IMAC for Metolachlor			
Parameter	**Value**	**Units**	**Notes/Source**
Noncancer Systemic Threshold Concentration	1.05	mg/L	Calculated above using 1990 IRIS RfD of 0.15 mg/kg-day
Concentration corresponding to Cancer Risk 10^{-6}	--	--	Not available
Taste Threshold Value	--	--	No threshold identified
Odor Threshold Value	--	--	No threshold identified
Maximum Contaminant Level (MCL)	--	--	USEPA (2023b)
National Secondary Drinking Water Standard	--	--	USEPA (2023b)
Lifetime Health Advisory Level (HAL)	0.7	mg/L	USEPA (2018)
Proposed Interim Maximum Allowable Concentration (IMAC)	0.7	mg/L	Lowest value selected; USEPA HAL.

Based on the review and calculations provided here, an IMAC of 0.7 mg/L is proposed for metolachlor, based on USEPA's lifetime HAL.

5. References

NCDEQ. 2022. North Carolina Department of Environmental Quality, Division of Water Resources Standard Operating Procedure for Establishing Interim Maximum Allowable Concentrations (IMACs) per 15A NCAC 02L .0202 (c). Revised April.

PubChem. 2023. Metolachlor Compound Summary. https://pubchem.ncbi.nlm.nih.gov/compound/4169. Accessed June 2023.

USEPA. 1995. Registration Eligibility Decision. Office of Prevention, Pesticides, and Toxic Substances. EPA 738-R-95-006. April.

USEPA. 2018. 2018 Edition of the Drinking Water Standards and Health Advisories Tables. EPA 822-F-18-001. Office of Water. USEPA. March.

USEPA. 2019. Metolachlor and S-Metolachlor: Draft Human Health Risk Assessment for Registration Review. Office of Chemical Safety and Pollution Prevention. September 19.

USEPA. 2023a. Integrated Risk Information System (IRIS) database [online]. Environmental Criteria and Assessment Office, US Environmental Protection Agency, Washington, DC. https://www.epa.gov/iris. Accessed June 2023.

USEPA. 2023b. National Primary Drinking Water Regulations and Secondary Drinking Water Regulations. https://www.epa.gov/sdwa. Accessed June 2023.

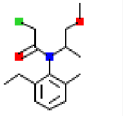
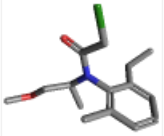
Attachment A

PubChem File

PubChem

COMPOUND SUMMARY

Metolachlor

PubChem CID	4169
Structure	 2D  3D Find Similar Structures
Chemical Safety	 Irritant  Environmental Hazard Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula	$C_{15}H_{22}ClNO_2$
Synonyms	metolachlor 51218-45-2 Yibingjiacaoan Pennant Codal More...
Molecular Weight	283.79
Dates	Modify 2023-05-05 Create 2005-03-25

Metolachlor is a tan to brown oily liquid with a slightly sweet odor. Slightly soluble in water and denser than water. Hence sinks in water. Soluble in most organic solvents. Used as a selective herbicide.

▸ CAMEO Chemicals

Widely used selective herbicides worldwide in corn, soybean and other crop cultures. Elevated concentrations of these herbicides and their degradation products have been detected in surface and groundwater. (A252) Metolachlor is an organic compound that is widely used as a herbicide. It is a derivative of aniline and is a member of the chloroacetanilide herbicides. It is highly effective toward grasses but its application is also controversial (L913).

▸ Toxin and Toxin Target Database (T3DB)

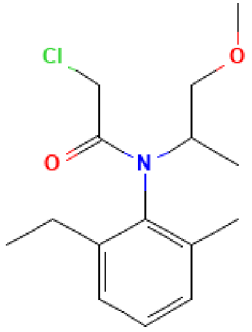
2-chloro-N-(2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl)acetamide is an organochlorine compound that is 2-chloroacetamide substituted by a (2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl) group at the nitrogen atom. It is an aromatic amide, an ether, a member of benzenes and an organochlorine compound.

ChEBI

1 Structures

1.1 2D Structure

Chemical Structure Depiction



PubChem

1.2 3D Conformer

PubChem

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(1-methoxypropan-2-yl)acetamide

Computed by Lexichem TK 2.7.0 (PubChem release 2021.05.07)

PubChem

2.1.2 InChI

InChI=1S/C15H22ClNO2/c1-5-13-8-6-7-11(2)15(13)17(14(18)9-16)12(3)10-19-4/h6-8,12H,5,9-10H2,1-4H3

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.3 InChIKey

WVQBLGZPHOPPFO-UHFFFAOYSA-N

Computed by InChI 1.0.6 (PubChem release 2021.05.07)

PubChem

2.1.4 Canonical SMILES

CCC1=CC=CC(=C1N(C(C)COC)C(=O)CCl)C

Computed by OEChem 2.3.0 (PubChem release 2021.05.07)

PubChem

2.2 Molecular Formula

C15H22ClNO2

CAMEO Chemicals; PubChem

$C_{15}H_{22}ClNO_2$

ILO International Chemical Safety Cards (ICSC)

2.3 Other Identifiers

2.3.1 CAS

51218-45-2

CAMEO Chemicals; CAS Common Chemistry; ChemIDplus; EPA DSSTox; European Chemicals Agency (ECHA); FDA Global Substance Registration System (GSRS); Hazardous Substances Data Bank (HSDB); ILO International Chemical Safety Cards (ICSC)

82535-90-8

ChemIDplus

2.3.2 Deprecated CAS

55762-76-0, 63150-68-5, 94449-58-8

ChemIDplus

164201-38-1

ChemIDplus

55762-76-0, 63150-68-5

EPA DSSTox

2.3.3 European Community (EC) Number

257-060-8

European Chemicals Agency (ECHA)

2.3.4 ICSC Number

1360

ILO International Chemical Safety Cards (ICSC)

2.3.5 RTECS Number

AN3430000

The National Institute for Occupational Safety and Health (NIOSH)

2.3.6 UNII

X0I01K05X2

FDA Global Substance Registration System (GSRS)

2.3.7 DSSTox Substance ID

DTXSID4022448

EPA DSSTox

2.3.8 Nikkaji Number

J1.898H

Japan Chemical Substance Dictionary (Nikkaji)

2.3.9 Wikipedia

Metolachlor

Wikipedia

2.3.10 Wikidata

Q409598

Wikidata

2.3.11 Metabolomics Workbench ID

67472

Metabolomics Workbench

2.4 Synonyms

2.4.1 MeSH Entry Terms

2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxyethyl)acetamide
metolachlor

Medical Subject Headings (MeSH)

2.4.2 Depositor-Supplied Synonyms

metolachlor	Dual 720EC	Humextra
51218-45-2	Dual 960 EC	Acetamide, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)-, s
Yibingjiacaoan	Dual 8E	82535-90-8
Pennant	2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide	Metolachlor technical
Codal	N-(1-Methyl-2-methoxyethyl)-N-chloroacetyl-2-ethyl-6-methylaniline	DTXCID402448
Dual	CGA-24705	Metolachlor, analytical standard
Dual Magnum	Acetamide, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)-	Metetilachlor
Dual Triple	CGA 24705	Metolachlore
2-chloro-N-(2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl)acetamide	DTXSID4022448	Jindual
Dual II	CHEBI:83645	Metoken

PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	283.79	Computed by PubChem 2.1 (PubChem release 2021.05.07)
XLogP3	3.1	Computed by XLogP3 3.0 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	0	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Rotatable Bond Count	6	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Exact Mass	283.1339066	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Monoisotopic Mass	283.1339066	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	29.5 $Å^2$	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Heavy Atom Count	19	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	285	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	1	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.05.07)

PubChem

3.2 Experimental Properties

3.2.1 Physical Description

Metolachlor is a tan to brown oily liquid with a slightly sweet odor. Slightly soluble in water and denser than water. Hence sinks in water. Soluble in most organic solvents. Used as a selective herbicide.

CAMEO Chemicals

Colorless liquid; [Merck Index] White to tan liquid; [HSDB]

Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

ODOURLESS CLEAR LIQUID.

ILO International Chemical Safety Cards (ICSC)

3.2.2 Color/Form

Colorless liquid

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1059

Hazardous Substances Data Bank (HSDB)

Colorless to tan liquid

MacBean C, ed. Metolachlor (51218-45-2). In: The e-Pesticide Manual, 15th Edition, Version 5.0.1 (2010). Surrey UK, British Crop Protection Council.

Hazardous Substances Data Bank (HSDB)

3.2.3 Boiling Point

212 °F at 0.001 mmHg (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

CAMEO Chemicals

BP: 100 °C at 0.001 mm Hg

Haynes, W.M. (ed.) CRC Handbook of Chemistry and Physics. 91st ed. Boca Raton, FL: CRC Press Inc., 2010-2011, p. 3-378

Hazardous Substances Data Bank (HSDB)

3.2.4 Melting Point

-62.1 °C

MacBean C, ed. Metolachlor (51218-45-2). In: The e-Pesticide Manual, 15th Edition, Version 5.0.1 (2010). Surrey UK, British Crop Protection Council.

Hazardous Substances Data Bank (HSDB); ILO International Chemical Safety Cards (ICSC)

3.2.5 Flash Point

greater than 230 °F (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

CAMEO Chemicals

Flashpoint of Dual 8E is 200 °F (Closed cup)

Weed Science Society of America. Herbicide Handbook. 5th ed. Champaign, Illinois: Weed Science Society of America, 1983., p. 313

Hazardous Substances Data Bank (HSDB)

190 °C

ILO International Chemical Safety Cards (ICSC)

3.2.6 Solubility

Miscible with benzene, toluene, ethanol, acetone, xylene, hexane, dimethylformamide, dichloroethane, cyclohexanone, methanol, octanol, and dichloromethane. Insoluble in ethylene glycol, propylene glycol, and petroleum ether.

MacBean C, ed. Metolachlor (51218-45-2). In: The e-Pesticide Manual, 15th Edition, Version 5.0.1 (2010). Surrey UK, British Crop Protection Council.

▸ Hazardous Substances Data Bank (HSDB)

Soluble in most organic solvents.

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1059

▸ Hazardous Substances Data Bank (HSDB)

In water, 530 mg/L at 20 °C

PMID:1732992

Wauchope RD et al; Rev Environ Contam Toxicol 123: 1-155 (1992)

▸ Hazardous Substances Data Bank (HSDB)

Solubility in water, mg/l at 25 °C: 488

▸ ILO International Chemical Safety Cards (ICSC)

3.2.7 Density

1.12 (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

▸ CAMEO Chemicals

1.12 g/cu cm at 20 °C

Lide, D.R., G.W.A. Milne (eds.). Handbook of Data on Organic Compounds. Volume I. 3rd ed. CRC Press, Inc. Boca Raton ,FL. 1994., p. V4: 3435

▸ Hazardous Substances Data Bank (HSDB)

1.12 g/cm³

▸ ILO International Chemical Safety Cards (ICSC)

3.2.8 Vapor Pressure

0.0000314 [mmHg]

▸ Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

3.14X10-5 mm Hg at 25 °C

PMID:1732992

Wauchope RD et al; Rev Environ Contam Toxicol 123: 1-155 (1992)

▸ Hazardous Substances Data Bank (HSDB)

Vapor pressure, Pa at 25 °C: 0.0042

ILO International Chemical Safety Cards (ICSC)

3.2.9 LogP

log Kow = 3.13

Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995., p. 135

Hazardous Substances Data Bank (HSDB)

2.9

ILO International Chemical Safety Cards (ICSC)

3.2.10 Henry's Law Constant

Henry's Law constant = 9.0X10-9 atm-cu m/mole at 20 °C

Chesters G et al; Environ Contam Toxicol 110: 1-74 (1989)

Hazardous Substances Data Bank (HSDB)

3.2.11 Stability/Shelf Life

Stable up to about 275 °C.

MacBean C, ed. Metolachlor (51218-45-2). In: The e-Pesticide Manual, 15th Edition, Version 5.0.1 (2010). Surrey UK, British Crop Protection Council.

Hazardous Substances Data Bank (HSDB)

On hydrolysis at 20 °C, 50% loss (calculated) occurs in >200 days at /a pH between 1 and 9/. Stable less than or equal to 300 °C.

Worthing, C.R. and S.B. Walker (eds.). The Pesticide Manual - A World Compendium. 8th ed. Thornton Heath, UK: The British Crop Protection Council, 1987., p. 568

Hazardous Substances Data Bank (HSDB)

Shelf life of the formulation is estimated to be 5 year minimum based on no significant decomposition at 70 °C for 3 weeks or at 50 °C for 20 weeks. There is no crystallization at temperatures below 0 °C.

Weed Science Society of America. Herbicide Handbook. 5th ed. Champaign, Illinois: Weed Science Society of America, 1983., p. 313

Hazardous Substances Data Bank (HSDB)

3.2.12 Autoignition Temperature

510 °F (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

CAMEO Chemicals

3.2.13 Decomposition

When heated to decompostion it emits toxic fumes of /**hydrogen chloride** and nitrogen oxides/.

Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2546

Hazardous Substances Data Bank (HSDB)

3.2.14 Corrosivity

Noncorrosive

Ahrens, W.H. Herbicide Handbook of the Weed Science Society of America. 7th ed. Champaign, IL: Weed Science Society of America, 1994., p. 198

Hazardous Substances Data Bank (HSDB)

3.2.15 Refractive Index

Index of refraction: 1.5301 at 20 °C/D

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1059

Hazardous Substances Data Bank (HSDB)

3.2.16 Collision Cross Section

161.46 Å^2 [M+H]$^+$ [CCS Type: DT, Method: stepped-field]

https://pubs.rsc.org/en/content/articlelanding/2017/sc/c7sc03464d

CCSbase

175.84 Å^2 [M+Na]$^+$ [CCS Type: DT, Method: stepped-field]

https://pubs.rsc.org/en/content/articlelanding/2017/sc/c7sc03464d

CCSbase

158.23 Å^2 [M+H]$^+$ [CCS Type: TW]

https://pubs.acs.org/doi/abs/10.1021/acs.analchem.7b00741

CCSbase

159.1 Å^2 [M+H]$^+$ [CCS Type: DT, Method: single field calibrated]

https://pubs.rsc.org/en/content/articlelanding/2018/ay/c7ay02808c

CCSbase

159.39 Å^2 [M+H]$^+$

171.44 Å^2 [M+Na]$^+$

S61 | UJICCSLIB | Collision Cross Section (CCS) Library from UJI | ***DOI:10.5281/zenodo.3549476***

NORMAN Suspect List Exchange

174.7 Å^2 [M+Na]$^+$

160.4 Å^2 [M+H]$^+$

S50 | CCSCOMPEND | The Unified Collision Cross Section (CCS) Compendium | ***DOI:10.5281/zenodo.2658162***

NORMAN Suspect List Exchange

3.2.17 Other Experimental Properties

Hydroxyl radical reaction rate constant = 7.02X10-11 cu cm/molec-sec at 25 °C (est)

Atkinson R; Environ Toxicol Chem 7: 435-62 (1988)

- Hazardous Substances Data Bank (HSDB)

3.2.18 Chemical Classes

Pesticides -> Herbicides, Chloracetanilide

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

4 Spectral Information

4.1 1D NMR Spectra

4.1.1 1H NMR Spectra

Instrument Name	Varian CFT-20
Copyright	Copyright © 2009-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

Instrument Name	Varian CFT-20
Copyright	Copyright © 2009-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

4.1.2 13C NMR Spectra

Source of Sample	H. Moser, Ciba-Geigy AG, Basel, Switzerland
Copyright	Copyright © 1980, 1981-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

Source of Sample	H. Moser, Ciba-Geigy AG, Basel, Switzerland
Copyright	Copyright © 1980, 1981-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

4.2 Mass Spectrometry

4.2.1 GC-MS

Showing 2 of 5 View More

NIST Number	125547
Library	Main library
Total Peaks	166
m/z Top Peak	162
m/z 2nd Highest	238
m/z 3rd Highest	45
Thumbnail	

NIST Mass Spectrometry Data Center

NIST Number	190405
Library	Replicate library
Total Peaks	138
m/z Top Peak	162
m/z 2nd Highest	238
m/z 3rd Highest	240
Thumbnail	

NIST Mass Spectrometry Data Center

4.2.2 MS-MS

Showing 2 of 7 View More

Spectra ID	2227849
Ionization Mode	Positive
SPLASH	splash10-0udi-0090000000-2d374f885d1a6109e24a
Top 5 Peaks	252.1148 100
Thumbnail	

Human Metabolome Database (HMDB)

Spectra ID	2231065
Ionization Mode	Positive
SPLASH	splash10-001l-2900000000-8a4678702e7a9f5cd538
Top 5 Peaks	91.0543 100 133.0886 71.41 132.0808 58.68 119.073 56.23 134.0964 54.64
Thumbnail	

Human Metabolome Database (HMDB)

4.2.3 LC-MS

Showing 2 of 38 View More

Accession ID	MSBNK-Athens_Univ-AU355601
Authors	Nikiforos Alygizakis, Nikolaos Thomaidis, University of Athens
Instrument	Bruker maXis Impact
Instrument Type	LC-ESI-QTOF
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	10 eV
Fragmentation Mode	CID
Column Name	Acclaim RSLC C18 2.2um, 2.1x100mm, Thermo
Retention Time	10.2 min
Precursor m/z	284.1412
Precursor Adduct	[M+H]+
Top 5 Peaks	284.1415 999 252.1151 926 254.1122 204 286.1392 170 253.1181 114
SPLASH	splash10-0ue9-0090000000-a96a62134f97c8990aa3
Thumbnail	

License	CC BY-SA

MassBank Europe

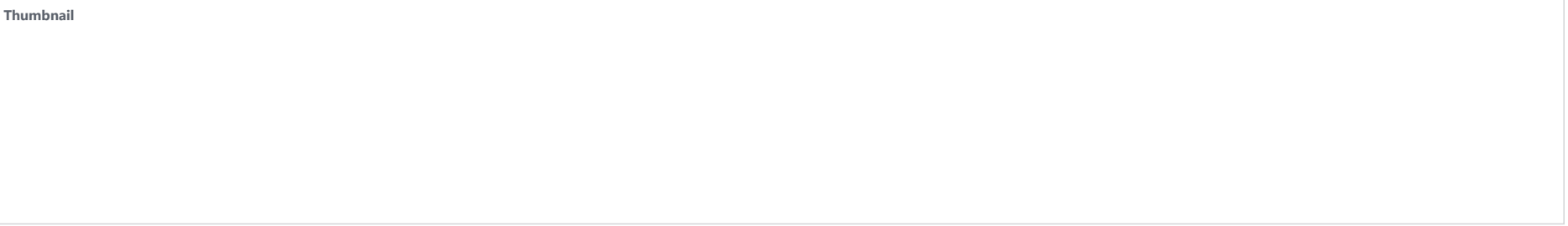
Accession ID	MSBNK-Athens_Univ-AU355602
Authors	Nikiforos Alygizakis, Nikolaos Thomaidis, University of Athens
Instrument	Bruker maXis Impact
Instrument Type	LC-ESI-QTOF
MS Level	MS2
Ionization Mode	POSITIVE
Ionization	ESI
Collision Energy	20 eV
Fragmentation Mode	CID
Column Name	Acclaim RSLC C18 2.2um, 2.1x100mm, Thermo
Retention Time	10.2 min
Precursor m/z	284.1412
Precursor Adduct	[M+H]+
Top 5 Peaks	252.1151 999 254.1122 209 253.1181 111 176.1427 81 255.1147 16
SPLASH	splash10-0udi-0090000000-90856c734035339a78f9
Thumbnail	

License	CC BY-SA

MassBank Europe

4.3 IR Spectra

4.3.1 FTIR Spectra

Technique	CAPILLARY CELL: NEAT
Source of Sample	H. MOSER, CIBA-GEIGY AG, BASEL, SWITZERLAND
Copyright	Copyright © 1980, 1981-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

Technique	CAPILLARY CELL: NEAT
Source of Sample	H. MOSER, CIBA-GEIGY AG, BASEL, SWITZERLAND
Copyright	Copyright © 1980, 1981-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

4.3.2 Vapor Phase IR Spectra

Instrument Name	DIGILAB FTS-14
Technique	Vapor Phase
Copyright	Copyright © 1980, 1981-2021 John Wiley & Sons, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

5 Related Records

5.1 Related Compounds with Annotation

PubChem

5.2 Related Compounds

Same Connectivity	6 Records
Same Stereo	3 Records
Same Isotope	3 Records
Same Parent, Connectivity	11 Records
Same Parent, Stereo	7 Records
Same Parent, Isotope	8 Records
Same Parent, Exact	5 Records
Mixtures, Components, and Neutralized Forms	314 Records
Similar Compounds	398 Records
Similar Conformers	75 Records

PubChem

5.3 Substances

5.3.1 Related Substances

All	544 Records
Same	159 Records

Mixture	385 Records

PubChem

5.3.2 Substances by Category

PubChem

5.4 Entrez Crosslinks

PubMed	440 Records
Taxonomy	13 Records
OMIM	10 Records
Gene	48 Records

PubChem

5.5 Associated Chemicals

S-Metolachlor; 87392-12-9

Hazardous Substances Data Bank (HSDB)

5.6 NCBI LinkOut

NCBI

6 Chemical Vendors

- PubChem

7 Drug and Medication Information

7.1 Clinical Trials

7.1.1 ClinicalTrials.gov

ClinicalTrials.gov

8 Agrochemical Information

8.1 Agrochemical Category

Herbicide

- EPA Pesticide Ecotoxicity Database

Pesticide active substances

- EU Pesticides Database

Herbicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | DOI:10.5281/zenodo.3862688

- NORMAN Suspect List Exchange

Pesticides -> Herbicides -> Amide herbicides -> Anilide herbicides -> Chloroacetanilide herbicides

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | DOI:10.5281/zenodo.3754448

- NORMAN Suspect List Exchange

8.2 Agrochemical Transformations

Metolachlor has known environmental transformation products that include Metolachlor-Morpholinone, Metolachlor ESA, and Metolachlor OXA.

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | DOI:10.5281/zenodo.3754448

- NORMAN Suspect List Exchange

8.3 EU Pesticides Data

Active Substance	metolachlor
Status	Not approved [Reg. (EC) No 1107/2009]
Legislation	2002/2076

- EU Pesticides Database

8.4 USDA Pesticide Data Program

Pesticide	Metolachlor
Blueberries, Cultivated,	EPA tolerance level: 0.40 [ppm]
Broccoli	EPA tolerance level: 0.60 [ppm]
Blueberries, Frozen	EPA tolerance level: 0.40 [ppm]
Cauliflower	EPA tolerance level: 0.60 [ppm]
Cantaloupe	EPA tolerance level: 0.50 [ppm]
Carrots	EPA tolerance level: 0.40 [ppm]

Eggplant	EPA tolerance level: 0.10 [ppm]
Green Beans	EPA tolerance level: 0.30 [ppm]
Collard Greens	EPA tolerance level: 1.8 [ppm]
Kiwi Fruit	EPA tolerance level: NT
Orange Juice	EPA tolerance level: NT
Sweet Bell Peppers	EPA tolerance level: 0.10 [ppm]
Radishes	EPA tolerance level: 0.30 [ppm]
Summer Squash	EPA tolerance level: 0.50 [ppm]
Tangerines	EPA tolerance level: NT
Tomato Paste	EPA tolerance level: 0.30 [ppm]
Winter Squash	EPA tolerance level: 0.50 [ppm]

▸ USDA Pesticide Data Program

9 Pharmacology and Biochemistry

9.1 MeSH Pharmacological Classification

Herbicides

Pesticides used to destroy unwanted vegetation, especially various types of weeds, grasses (POACEAE), and woody plants. Some plants develop HERBICIDE RESISTANCE. (See **all compounds classified as Herbicides**.)

▸ **Medical Subject Headings (MeSH)**

9.2 Absorption, Distribution and Excretion

S-metolachlor is extensively absorbed and metabolized following oral administration. Elimination is via the urine and feces. Tissue residues were highest in whole blood. /**s-metolachlor**/

*USEPA; s-Metolachlor: s-Metolachlor Aggregate Human Health Risk Assessment. Document ID: EPA-HQ-OPP-2006-0292 p. 16 (July 13, 2006). Available from, as of February 3, 2012: **https://www.regulations.gov/#!home***

▸ **Hazardous Substances Data Bank (HSDB)**

Selective herbicide, absorbed predominantly by the hypocotyls and shoots.

Hartley, D. and H. Kidd (eds.). The Agrochemicals Handbook. 2nd ed. Lechworth, Herts, England: The Royal Society of Chemistry, 1987., p. A278/Aug 87

▸ **Hazardous Substances Data Bank (HSDB)**

Rats were administered a single oral dose (28.6 or 52.4 mg/kg) of metolachlor (purity not specified, but (14)C labeled and unlabeled metolachlor were synthesized for these experiments). The chemical was readily absorbed, since 70 to 90% of the metolachlor was excreted as metabolites within 48 hr.

USEPA; Health Advisories for 50 Pesticides p.617 (1988) NTIS PB88-245931

▸ **Hazardous Substances Data Bank (HSDB)**

Data from rats given radioactive metolachlor (approximately 3.2 to 3.5 mg/kg) orally demonstrated that the chemical is rapidly metabolized. Residues in meat tissue and blood were very low and only blood contained residue levels in excess of 0.1 ppm.

USEPA; Health Advisories for 50 Pesticides p.618 (1988) NTIS PB88-245931

▸ **Hazardous Substances Data Bank (HSDB)**

For more Absorption, Distribution and Excretion (Complete) data for METOLACHLOR (6 total), please visit the **HSDB record page**.

▸ **Hazardous Substances Data Bank (HSDB)**

9.3 Metabolism/Metabolites

METABOLISM IN PLANTS AFTER PREEMERGENCE APPLICATION OF METOLACHLOR APPEARS TO PROCEED BY NATURAL PRODUCT CONJUGATION OF THE ACETYL-CHLORO GROUP WITH THIS BOND LINKAGE PREDOMINANT OVER OXO. FURTHER REACTION OCCURS AT THE ETHER GROUP WITH HYDROLYSIS FOLLOWED BY SUGAR CONJUGATION. FINAL METABOLITES ARE RESULTS OF DISCONJUGATION, AND ARE POLAR, AQUEOUS SOLUBLE, NONVOLATILE AS WELL AS SENSITIVE TO DEGRADATION. HYDROLYSIS PROCEDURES CONVERT THE OXO-METABOLITES TO THE DEACETYLATED DERIVATIVE AND THE THIO-METABOLITES TO A **MORPHOLINE** DERIVATIVE.

Weed Science Society of America. Herbicide Handbook. 5th ed. Champaign, Illinois: Weed Science Society of America, 1983., p. 314

▸ **Hazardous Substances Data Bank (HSDB)**

STUDIES WITH THE **ANTOR** ANALOG METOLACHLOR (DUAL) WERE ALSO CONDUCTED WITH THE FUNGUS CHAETOMIUM GLOBOSUM. COMPOUNDS PRODUCED BY THIS ORGANISM WHEN INCUBATED WITH METOLACHLOR ARE: **2-CHLORO-N-(2-ETHYL-6- METHYLPHENYL)-N-(2-HYDROXY-1-METHYLETHYL)ACETAMIDE**; **2-CHLORO-N-(2-ETHYL- 6-METHYLPHENYL)ACETAMIDE**; N-(2-METHOXY-1-METHYLETHYL)-2-METHYL-

6-VINYLANILINE; N-(2-METHOXY-1-METHYLETHYL)-2,3-DIHYDRO-7-METHYLINDOLE; 8-ETHYL-3-HYDROXY- N-(2-METHOXY-1-METHYLETHYL)-2-OXO-1,2,3,4-TETRAHYDROQUINOLINE; 8-ETHYL-3- HYDROXY-N-ISOPROPYL-2-OXO-1,2,3,4-TETRAHYDROQUINOLINE; 2-HYDROXY-N-(2- METHOXY-1-METHYLETHYL)-N-(2-METHYL-6-VINYLPHENYL)ACETAMIDE; N-(2-METHOXY- 1-METHYLETHYL)-8-METHYL-2-OXO-1,2,3,4-TETRAHYDROQUINOLINE.

Menzie, C.M. Metabolism of Pesticides-Update III. Special Scientific Report- Wildlife No. 232. Washington, DC: U.S.Department of the Interior, Fish and Wildlife Service, 1980., p. 30

▸ Hazardous Substances Data Bank (HSDB)

IN FUNGI, ALPHA-CHLORINE ATOMS OF THESE PESTICIDES /INCLUDING METOLACHLOR/ ARE NOT DISPLACED BY SULFHYDRYL GROUPS BUT BY HYDROXYL GROUPS ALTHOUGH THE CHLORINE ATOM OF PROPACHLOR IS DISPLACED BY A SULFHYDRYL GROUP IN THE FIRST DEGRADATION STEP IN PLANTS. DEALKYLATION, DEACYLATION, AND RING FORMATION TO FORM INDOLINES AND QUINOLINES OCCUR IN FUNGI.

Aizawa, H. Metabolic Maps of Pesticides. New York, NY: Academic Press, 1982., p. 9

▸ Hazardous Substances Data Bank (HSDB)

Studies conducted to identify urinary and fecal metabolites in the rat indicated that metolachlor is metabolized via dechlorination, o-methylation, N-dealkylation and side-chain oxidation. Urinary metabolites included 2-ethyl-6-methylhydroxyacetanilide and N-(2-ethyl-6-methyl- phenyl)-N-(hydroxyacetyl)-DL-alanine). Fecal metabolites included 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-l-methylethyl) and N-(2-ethyl-6-methylphenyl)-N-(hydroxyacetyl)-DL-alamine).

USEPA; Health Advisories for 50 Pesticides p.618 (1988) NTIS PB88-245931

▸ Hazardous Substances Data Bank (HSDB)

For more Metabolism/Metabolites (Complete) data for METOLACHLOR (10 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

Metolachlor is metabolized via dechlorination, o-methylation, N-dealkylation and side-chain oxidation. Glutathione transferases mediathe the conjugation of metolachlor with with glutathione. Urinary metabolites included 2-ethyl-6-methylhydroxyacetanilide and N-(2-ethyl-6-methyl- phenyl)-N-(hydroxyacetyl)-DL-alanine). Fecal metabolites included 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-l-methylethyl) and N-(2-ethyl-6-methylphenyl)-N-(hydroxyacetyl)-DL-alamine). Metolachlor is also excreted in urine. (A571, A270)

▸ Toxin and Toxin Target Database (T3DB)

9.4 Transformations

▸ NORMAN Suspect List Exchange

10 Use and Manufacturing

10.1 Uses

EPA CPDat Chemical and Product Categories

*The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products, Scientific Data, volume 5, Article number: 180125 (2018), **DOI:10.1038/sdata.2018.125***

▸ **EPA Chemical and Products Database (CPDat)**

Sources/Uses

Used to control weeds in crops of corn, soybeans, peanuts, sorghum, potatoes, peas, cotton, safflower, stone fruits, nut trees, and ornamentals; also used on roadways; [EXTOXNET] Used in corn, peanuts, and soybeans; [Krieger, p. 1762]

Krieger - Krieger R (ed). Hayes' Handbook of Pesticide Toxicology, 3rd Ed. San Diego: Elsevier, 2010., p. 1762

▸ **Haz-Map, Information on Hazardous Chemicals and Occupational Diseases**

Industrial Processes with risk of exposure

Farming (Pesticides) [Category: Industry]

▸ **Haz-Map, Information on Hazardous Chemicals and Occupational Diseases**

For metolachlor (USEPA/OPP Pesticide Code: 108801) ACTIVE products with label matches. /SRP: Registered for use in the U.S. but approved pesticide uses may change periodically and so federal, state and local authorities must be consulted for currently approved uses./

*National Pesticide Information Retrieval System's USEPA/OPP Chemical Ingredients Database on Metolachlor (51218-45-2). Available from, as of December 21, 2011: **https://npirspublic.ceris.purdue.edu/ppis/***

▸ **Hazardous Substances Data Bank (HSDB)**

Herbicide

Crop Protection Handbook Volume 98, Meister Media Worldwide, Willoughby, OH 2012, p. 536

▸ **Hazardous Substances Data Bank (HSDB)**

Preemergence and preplant incorporated weed control

Crop Protection Handbook Volume 98, Meister Media Worldwide, Willoughby, OH 2012, p. 536

Hazardous Substances Data Bank (HSDB)

Control of annual grasses and some broad-leaved weeds ... Often used in combination with broad-leaved herbicides, to extend the spectrum of activity.

MacBean C, ed. Metolachlor (51218-45-2). In: The e-Pesticide Manual, 15th Edition, Version 5.0.1 (2010). Surrey UK, British Crop Protection Council.

Hazardous Substances Data Bank (HSDB)

S-metolachlor is a chloroactanilide herbicide, classified as a seedling shoot growth inhibitor. /S-Metolachlor/

USEPA/Office of Pesticide Programs; Ecological Risk Assessment for Use of S-Metolachlor (PC 108800) on Pumpkins and Winter Squash. p.11 Identification Number: EPA-HQ-OPP-2009-0081-0191 (May 2006). Available from, as of March 26, 2012: https://www.regulations.gov/#!home

Hazardous Substances Data Bank (HSDB)

Metolachlor is used for grass and broadleaf weed control in corn, soybean, peanuts, sorghum, and cotton. It is also used in combination with other herbicides. It been detected in ground and surface waters and concentrations ranging from 0.08 to 4.5 parts per billion (ppb) throughout the U.S. Evidence of the bioaccumulation of metolachlor in edible species of fish as well as its adverse effect on the growth and development raise concerns on its effects on human health. (L913).

Toxin and Toxin Target Database (T3DB)

10.1.1 Use Classification

Agrochemicals -> Pesticides

EU Pesticides Database

Hazard Classes and Categories -> Carcinogens

NJDOH RTK Hazardous Substance List

Herbicides

S69 | LUXPEST | Pesticide Screening List for Luxembourg | DOI:10.5281/zenodo.3862688

NORMAN Suspect List Exchange

Pesticides -> Herbicides -> Amide herbicides -> Anilide herbicides -> Chloroacetanilide herbicides

S66 | EAWAGTPS | Parent-Transformation Product Pairs from Eawag | DOI:10.5281/zenodo.3754448

NORMAN Suspect List Exchange

HERBICIDES

USGS Columbia Environmental Research Center

10.2 Methods of Manufacturing

(A) A mixture of 540 g (4.0 mols) of 2-ethyl-6-methylaniline and 306 g (2.0 moles) of 2-bromo-1-methoxypropane is heated for 40 hours at reduced pressure (10 mmHg) to 120 °C with stirring. After it has cooled, the light red, viscous solution is diluted with 200 mL of water and made alkaline with 210 mL of concentrated sodium hydroxide solution. The precipitated product is taken up in ether, and the ethereal solution is washed neutral with water, dried, and evaporated. Distillation of the residue yields pure-2-ethyl-6-methyl-N-[1'-methoxy-prop-2'-yl]-aniline which boils at 64 deg to 66 °C/0.07 Torr. (B) A solution of 9.7 g (0.047 mol) of the intermediate described under (A) and 5.05 g (0.05 mol) of triethylamine in 30 mL of benzene is treated dropwise with a solution of 5.65 g (0.05 mol) of chloroacetyl chloride in 10 mL of absolute benzene, and the mixture is further

stirred for 2 hours at room temperature. The reaction mixture is diluted with ether, the solution repeatedly washed with water, and dried. The solvent mixture is evaporated off in vacuo to give pure-2-ethyl-6-methyl-N-[1'-methoxy-prop-2'-yl]-chloroacetanilide.

Sittig, M. (ed.) Pesticide Manufacturing and Toxic Materials Control Encyclopedia. Park Ridge, NJ: Noyes Data Corporation. 1980., p. 525

Hazardous Substances Data Bank (HSDB)

Preparation: C. Vogel, R. Aebi, DE 2328340; eidem, US 3937730 (1973, 1976 both to Ciba-Geigy).

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 2006., p. 1059

Hazardous Substances Data Bank (HSDB)

10.3 Formulations/Preparations

USEPA/OPP Pesticide Code 108801; Trade Names: Milocep; Dual; CGA-24705; Bicep; codal; Cotoran multi; Primagram; Primextra; Pennant; and Ontrack 8E.

U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Metolachlor (51218-45-2). Available from, as of Sept 8, 2000: https://npirspublic.ceris.purdue.edu/ppis/

Hazardous Substances Data Bank (HSDB)

Premix Partners: Atrazine; Chloridazon; Metribuzin.

Crop Protection Handbook Volume 98, Meister Media Worldwide, Willoughby, OH 2012, p. 536

Hazardous Substances Data Bank (HSDB)

Formulation types: Emulsifiable concentrate, granule, smoke pellet, suspension concentrate

Tomlin, C.D.S. (ed.). The Pesticide Manual - World Compendium, 11 th ed., British Crop Protection Council, Surrey, England 1997, p. 834

Hazardous Substances Data Bank (HSDB)

Technical Metolachlor II (Agan Chem MFG, LTD): Metolachlor 96.8%.

Purdue University; National Pesticide Information Retrieval System, Metolachlor (51218-45-2), PC Code: 108801. Available from, as of February 3, 2012: https://npirspublic.ceris.purdue.edu/ppis/

Hazardous Substances Data Bank (HSDB)

For more Formulations/Preparations (Complete) data for METOLACHLOR (27 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

10.4 Consumption Patterns

(1992) 6X10+7 lbs

USGS; Pesticide 1992 Annual Use Map (Metolachlor). Nation Water Quality Assessment, Pesticide Synthesis Project, US Geological Survey. Available from, as of Sept 28, 2000: https://ca.water.usgs.gov/pnsp/use92/

Hazardous Substances Data Bank (HSDB)

10.5 General Manufacturing Information

The WHO Recommended Classification of Pesticides by Hazard identifies metolachlor (technical grade) as Class III: slightly hazardous; Main Use: herbicide.

WHO International Programme on Chemical Safety; The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009 p.36 (2010)

Hazardous Substances Data Bank (HSDB)

11 Identification

11.1 Analytic Laboratory Methods

Method: USGS-NWQL O-3106-93; Procedure: gas chromatography; Analyte: metolachlor; Matrix: water and mixtures of water-suspended sediment; Detection Limit: 0.2 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Metolachlor (51218-45-2). Available from, as of February 9, 2012: https://www.nemi.gov

Hazardous Substances Data Bank (HSDB)

Method: USGS-NWQL O-1433-01; Procedure: gas chromatography/mass spectrometry; Analyte: metolachlor; Matrix: filtered wastewater and natural-water samples; Detection Limit: 0.08 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Metolachlor (51218-45-2). Available from, as of February 9, 2012: https://www.nemi.gov

Hazardous Substances Data Bank (HSDB)

Method: USGS-NWQL O-1126-95; Procedure: gas chromatography-mass spectrometry with select-ion monitoring; Analyte: metolachlor; Matrix: natural water; Detection Limit: 0.009 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Metolachlor (51218-45-2). Available from, as of February 9, 2012: https://www.nemi.gov

Hazardous Substances Data Bank (HSDB)

Method: USGS-NWQL O-1121-91; Procedure: gas chromatography-mass spectrometry; Analyte: metolachlor; Matrix: natural water; Detection Limit: 0.097 ug/L.

National Environmental Methods Index; Analytical, Test and Sampling Methods. Metolachlor (51218-45-2). Available from, as of February 9, 2012: https://www.nemi.gov

Hazardous Substances Data Bank (HSDB)

For more Analytic Laboratory Methods (Complete) data for METOLACHLOR (19 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

11.2 NIOSH Analytical Methods

CHLORINATED AND ORGANONITROGEN HERBICIDES (AIR SAMPLING) 5602

NIOSH Manual of Analytical Methods

CHLORINATED AND ORGANONITROGEN HERBICIDES (HAND WASH) 9200

NIOSH Manual of Analytical Methods

CHLORINATED AND ORGANONITROGEN HERBICIDES (PATCH) 9201

NIOSH Manual of Analytical Methods

12 Safety and Hazards

12.1 Hazards Identification

12.1.1 GHS Classification

Showing 1 of 2 View More

Pictogram(s)	 Irritant; Environmental Hazard
Signal	Warning
GHS Hazard Statements	H303: May be harmful if swallowed [Warning Acute toxicity, oral] H317: May cause an allergic skin reaction [Warning Sensitization, Skin]
Precautionary Statement Codes	P261, P272, P280, P301+P317, P302+P352, P321, P333+P313, P362+P364, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)

▸ NITE-CMC

12.1.2 Hazard Classes and Categories

Showing 2 of 3 View More

Acute toxicity (Oral) - Category 5

Skin sensitization - Category 1

Hazardous to the aquatic environment (Acute) - Category 1

Hazardous to the aquatic environment (Long-term) - Category 1

▸ NITE-CMC

Skin sensitization - Category 1

Specific target organ toxicity - Single exposure - Category 1 (central nervous system)

Hazardous to the aquatic environment (Acute) - Category 1

Hazardous to the aquatic environment (Long-term) - Category 1

▸ NITE-CMC

12.1.3 Health Hazards

Can cause skin irritation and eye irritation. Headache and nausea may occur following prolong exposure. (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

▸ CAMEO Chemicals

12.1.4 Fire Hazards

Combustible.

- ILO International Chemical Safety Cards (ICSC)

12.1.5 Hazards Summary

Classified as 'slightly toxic, metolachlor is an pre-emergent herbicide with an oral LD50 of 2780 mg/kg. [EXTOXNET] Methemoglobinemia has been reported after poisoning by ingestion. [HSDB] No listed effects of short-term or long-term exposure; [ICSC] A strong skin sensitizer; Increased incidence of liver tumors in female rats; No developmental toxicity; Reduced pup weights in reproductive study with no toxicity in parental animals; [Krieger, p. 1762-3]

Krieger - Krieger R (ed). Hayes' Handbook of Pesticide Toxicology, 3rd Ed. San Diego: Elsevier, 2010., p. 1762-3

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

12.1.6 Fire Potential

This chemical is a combustible liquid. ...

Sittig, M. Handbook of Toxic and Hazardous Chemicals and Carcinogens, 2002. 4th ed.Vol 1 A-H Norwich, NY: Noyes Publications, 2002., p. 1618

- Hazardous Substances Data Bank (HSDB)

12.1.7 Skin, Eye, and Respiratory Irritations

Skin ... eye and mucous membrane irritation.

USEPA; Health Advisories for 50 Pesticides p.618 (1988) NTIS PB88-245931

- Hazardous Substances Data Bank (HSDB)

12.2 First Aid Measures

12.2.1 First Aid

INHALATION: Call for medical aid. Move victim from contaminated area to fresh air. Apply artificial respiration if necessary. INGESTION: If victim is conscious administer 1,2 glasses of water and induce vomiting. EYES: Immediately rinse with large amounts of running water. Do not apply any medication, unless advised by a physician. SKIN: Wash with soap and plenty of water including hair and undernails. Do not apply any medication except on the advice of a physician. Remove clothing and wash before reuse. (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

- CAMEO Chemicals

12.2.2 Inhalation First Aid

Fresh air, rest.

- ILO International Chemical Safety Cards (ICSC)

12.2.3 Skin First Aid

Rinse and then wash skin with water and soap.

- ILO International Chemical Safety Cards (ICSC)

12.2.4 Eye First Aid

First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then refer for medical attention.

- ILO International Chemical Safety Cards (ICSC)

12.2.5 Ingestion First Aid

Give one or two glasses of water to drink. Refer for medical attention .

- ILO International Chemical Safety Cards (ICSC)

12.3 Fire Fighting

Fire Extinguishing Agents: Dry chemical, alcohol foam or carbon dioxide (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

- CAMEO Chemicals

Use dry sand, alcohol-resistant foam, carbon dioxide.

- ILO International Chemical Safety Cards (ICSC)

12.3.1 Fire Fighting Procedures

Dry sand, alcohol-resistant foam, carbon dioxide.

International Program on Chemical Safety/Commission of the European Communities; International Chemical Safety Card on Metolachlor (October 2000). Available from, as of August 23, 2012: ***https://www.inchem.org/pages/icsc.html***

- Hazardous Substances Data Bank (HSDB)

... Use dry chemical, carbon dioxide, or alcohol foam extinguishers. ...

Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 5th Edition Volume 1: A-H,Volume 2: I-Z. William Andrew, Norwich, NY 2008, p. 1761

- Hazardous Substances Data Bank (HSDB)

Wear full protective clothing and self-contained breathing apparatus. Evacuate nonessential personnel from the area to prevent human exposure to fire, smoke, fumes or products of combustion. Prevent use of contaminated buildings, area, and equipment until decontaminated. Stay upwind. Minimize runoff. /Me-Too-Lachlor Herbicide/

Drexel Chemical Company; MSDS for Me-Too-Lachlor Herbicide, Last Revision Date: 5/27/2010. Available from, as of March 22, 2012: ***https://www.drexchem.com/products/MSDS/Me-Too-Lachlor.pdf***

- Hazardous Substances Data Bank (HSDB)

12.3.2 Firefighting Hazards

... Vapors in confined areas may explode when exposed to fire. Containers may explode in fire. Storage containers may rocket great distances, in many directions. ...

Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 5th Edition Volume 1: A-H,Volume 2: I-Z. William Andrew, Norwich, NY 2008, p. 1761

Hazardous Substances Data Bank (HSDB)

12.4 Accidental Release Measures

12.4.1 Spillage Disposal

Do NOT let this chemical enter the environment. Collect leaking and spilled liquid in covered containers as far as possible. Then store and dispose of according to local regulations. Personal protection: P2 filter respirator for harmful particles.

ILO International Chemical Safety Cards (ICSC)

12.4.2 Cleanup Methods

... Remove all ignition sources. Ventilate area of spill or leak. Absorb liquids in vermiculite, dry sand, earth, peat, carbon, or a similar material and deposit in sealed containers. Keep this chemical out of a confined space such as a sewer, because of the possibility of an explosion, unless the sewer is designed to prevent the build-up of explosive concentrations. ...

Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 5th Edition Volume 1: A-H,Volume 2: I-Z. William Andrew, Norwich, NY 2008, p. 1761

Hazardous Substances Data Bank (HSDB)

Numerous pesticides were monitored in surface waters in agricultural areas. Atrazine, alachlor, metolachlor, cyanazine, metribuzin, carbofuran, linuron, and simazine were found in the influent to three water treatment plants in storm runoff following their application. Studies at these plants, together with bench-scale studies, demonstrated poor control by conventional treatment processes. The relatively high adsorption capacities of these agrichemicals indicate that granular activated carbon can be cost effective for their control. Powered activated carbon applied at taste and odor control doses can also be effective if moderate percent removal is required.

Miltner RJ et al; Govt Reports Announcements & Index (GRA&I) Issue 20: (1988)

Hazardous Substances Data Bank (HSDB)

For small spills, cover the spill with an absorbent material such as pet litter. Sweep up and place in an approved chemical container. Wash the spill area with water containing a strong detergent, absorb with pet litter or other absorbent material, sweep up and place in a chemical container. Seal the container and handle in an approved manner. Flush the area with water to remove any residue. Do not allow wash water to contaminate water supplies. /Me-Too-Lachlor Herbicide/

*Drexel Chemical Company; MSDS for Me-Too-Lachlor Herbicide, Last Revision Date: 5/27/2010. Available from, as of March 22, 2012: **https://www.drexchem.com/products/MSDS/Me-Too-Lachlor.pdf***

Hazardous Substances Data Bank (HSDB)

Large spills should be dammed-off and pumped into containers; soak up remainder with absorbent material and dispose of in accordance with local regulations.

Crop Protection Handbook Volume 98, Meister Media Worldwide, Willoughby, OH 2012, p. 536

Hazardous Substances Data Bank (HSDB)

For more Cleanup Methods (Complete) data for METOLACHLOR (7 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.4.3 Disposal Methods

SRP: The most favorable course of action is to use an alternative chemical product with less inherent propensity for occupational harm/injury/toxicity or environmental contamination. Recycle any unused portion of the material for its approved use or return it to the manufacturer or supplier. Ultimate disposal of the chemical must consider: the material's impact on air quality; potential migration in soil or water; effects on animal and plant life; and conformance with environmental and public health regulations.

Hazardous Substances Data Bank (HSDB)

SRP: Wastewater from contaminant suppression, cleaning of protective clothing/equipment, or contaminated sites should be contained and evaluated for subject chemical or decomposition product concentrations. Concentrations shall be lower than applicable environmental discharge or disposal criteria. Alternatively, pretreatment and/or discharge to a permitted wastewater treatment facility is acceptable only after review by the governing authority and assurance that "pass through" violations will not occur. Due consideration shall be given to remediation worker exposure (inhalation, dermal and ingestion) as well as fate during treatment, transfer and disposal. If it is not practicable to manage the chemical in this fashion, it must be evaluated in accordance with EPA 40 CFR Part 261, specifically Subpart B, in order to determine the appropriate local, state and federal requirements for disposal.

▸ Hazardous Substances Data Bank (HSDB)

Must be disposed of by special means, e.g., suitable incineration, in accordance with local regulations.

Crop Protection Handbook Volume 98, Meister Media Worldwide, Willoughby, OH 2012, p. 536

▸ Hazardous Substances Data Bank (HSDB)

Group I Containers: Combustible containers from organic or metallo-organic pesticides (except organic **mercury**, lead, **cadmium**, or **arsenic** compounds) should be disposed of in pesticide incinerators or in specified landfill sites. /Organic or metallo-organic pesticides/

40 CFR 165.9(a) (7/1/90)

▸ Hazardous Substances Data Bank (HSDB)

For more Disposal Methods (Complete) data for METOLACHLOR (8 total), please visit the **HSDB record page**.

▸ Hazardous Substances Data Bank (HSDB)

12.4.4 Preventive Measures

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. /Me-Too-Lachlor Herbicide/

*Drexel Chemical Company; Product Label for Me-Too-Lachlor Herbicide. Available from, as of March 22, 2012: **https://www.drexchem.com/products/Labels/548SP-0310asterisk.pdf***

▸ Hazardous Substances Data Bank (HSDB)

For terrestrial uses, do not apply directly to **water**, to areas where surface **water** is present or to intertidal areas below the mean high **water** mark. /Me-Too-Lachlor Herbicide/

*Drexel Chemical Company; Product Label for Me-Too-Lachlor Herbicide. Available from, as of March 22, 2012: **https://www.drexchem.com/products/Labels/548SP-0310asterisk.pdf***

▸ Hazardous Substances Data Bank (HSDB)

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. /Me-Too-Lachlor Herbicide/

*Drexel Chemical Company; Product Label for Me-Too-Lachlor Herbicide. Available from, as of March 22, 2012: **https://www.drexchem.com/products/Labels/548SP-0310asterisk.pdf***

▸ Hazardous Substances Data Bank (HSDB)

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 24 hours. Exception: If the product is soil-injected or soil-incorporated, the Worker Protection Standard, under certain circumstances, allows workers to enter the treated area if there will be no contact with anything that has been treated. /Me-Too-Lachlor Herbicide/

*Drexel Chemical Company; Product Label for Me-Too-Lachlor Herbicide. Available from, as of March 22, 2012: **https://www.drexchem.com/products/Labels/548SP-0310asterisk.pdf***

▸ Hazardous Substances Data Bank (HSDB)

For more Preventive Measures (Complete) data for METOLACHLOR (15 total), please visit the **HSDB record page**.

▸ Hazardous Substances Data Bank (HSDB)

12.5 Handling and Storage

12.5.1 Safe Storage

Separated from food and feedstuffs. Well closed. Provision to contain effluent from fire extinguishing.

- ILO International Chemical Safety Cards (ICSC)

12.5.2 Storage Conditions

Do not contaminate water, food or feed by storage ... Keep container closed to prevent spills and contamination. Store in original container. /Me-Too-Lachlor Herbicide/

Drexel Chemical Company; Product Label for Me-Too-Lachlor Herbicide. Available from, as of March 22, 2012: https://www.drexchem.com/products/Labels/548SP-0310asterisk.pdf

- Hazardous Substances Data Bank (HSDB)

Store above -30 °F.

Crop Protection Handbook Volume 98, Meister Media Worldwide, Willoughby, OH 2012, p. 536

- Hazardous Substances Data Bank (HSDB)

Store in tightly closed containers in a cool, well ventilated area away from oxidizers. Where possible, automatically pump liquid from drums or other storage containers to porcess containers.

Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 5th Edition Volume 1: A-H,Volume 2: I-Z. William Andrew, Norwich, NY 2008, p. 1761

- Hazardous Substances Data Bank (HSDB)

Safe Storage of Pesticides. Always store pesticides in their original containers, complete with labels that list ingredients, directions for use, and first aid steps in case of accidental poisoning. Never store pesticides in cabinets with or near food, animal feed, or medical supplies. Do not store pesticides in places where flooding is possible or in places where they might spill or leak into wells, drains, ground water, or surface water. /Residential users/

USEPA/Prevention, Pesticides, and Toxic Substances; Citizen's Guide to Pest Control and Pesticide Safety p.23 (March 2005) EPA 730-K-04-002

- Hazardous Substances Data Bank (HSDB)

12.6 Exposure Control and Personal Protection

12.6.1 Inhalation Risk

Evaporation at 20 °C is negligible; a harmful concentration of airborne particles can, however, be reached quickly on spraying.

- ILO International Chemical Safety Cards (ICSC)

12.6.2 Acceptable Daily Intakes

OPP RfD= 0.15 mg/kg; EPA RfD= 0.15 mg/kg.

USEPA/OPP; Health Effects Div RfD/ADI Tracking Report p.39 (8/26/91)

- Hazardous Substances Data Bank (HSDB)

12.6.3 Allowable Tolerances

Tolerances are established for the combined residues (free and bound) of the herbicide metolachlor, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide, and its metabolites, determined as the derivatives, 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound in the following raw agricultural commodities:

Commodity	Parts per million
Almond, hulls	0.30
Animal feed, nongrass, group 18	1.0
Cattle, fat	0.02
Cattle, kidney	0.20
Cattle, liver	0.05
Cattle, meat	0.02
Cattle, meat byproducts, except kidney and liver	0.04
Corn, field, forage	6.0
Corn, field, grain	0.10
Corn, field, stover	6.0
Corn, sweet, forage	6.0
Corn, sweet, kernel plus cob with husks removed	0.10
Corn, sweet, stover	6.0
Cotton, gin byproducts	4.0
Cotton, undelinted seed	0.10
Dillweed	0.50
Egg	0.02
Goat, fat	0.02
Goat, kidney	0.20
Goat, liver	0.05
Goat, meat	0.02
Goat, meat byproducts, except kidney and liver	0.04
Grass, forage	10
Grass, hay	0.20
Horse, fat	0.02
Horse, kidney	0.20
Horse, liver	0.05
Horse, meat	0.02
Horse, meat byproducts, except kidney and liver	0.04
Milk	0.02
Nut, tree, group 14	0.10
Okra	0.50
Peanut	0.20
Peanut, hay	20
Peanut, meal	0.40
Potato	0.20
Poultry, fat	0.02
Poultry, meat	0.02

Commodity	Parts per million
Poultry, meat byproducts	0.05
Safflower, seed	0.10
Sheep, fat	0.02
Sheep, kidney	0.20
Sheep, liver	0.05
Sheep, meat	0.02
Sheep, meat byproducts, except kidney and liver	0.04
Sorghum, grain, forage	1.0
Sorghum, grain, grain	0.30
Sorghum, grain, stover	4.0
Soybean, forage	5.0
Soybean, hay	8.0
Soybean, seed	0.20
Tomato	0.10
Vegetable, foliage of legume, subgroup 7A, except soybean	15.0
Vegetable, legume, group 6	0.30

40 CFR 180.368(a)(1) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: ***https://www.ecfr.gov***

▶ Hazardous Substances Data Bank (HSDB)

Tolerances are established for residues of **S-metolachlor**, including its metabolites and degradates, in or on the commodity(s), as defined. Compliance with the tolerance levels specified in the following table below is to be determined by measuring only the sum of free and bound **S-metolachlor**, S-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide, its R-enantiomer, and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and **4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone**, calculated as the stoichiometric equivalent of **S-metolachlor**, in or on the commodity. /**S-Metolachlor**/

Commodity	Parts per million
Aspaagus	0.10
Beet, sugar, molasses	2.0
Beet, sugar, roots	0.5
Beet, sugar, tops	15.0
Brassica, head and stem, subgroup 5A	0.60
Brassica, leafy greens, subgroup 5B	1.8
Bushberry subgroup 13-07B	0.15
Caneberry subgroup 13-07A	0.10
Carrot, roots	0.40
Cattle, fat	0.02
Cattle, kidney	0.20
Cattle, liver	0.05
Cattle, meat	0.02
Cattle, meat byproducts, except kidney and liver	0.04

Commodity	Parts per million
Corn, field, grain	0.10
Corn, field, forage	6.0
Corn, field, stover	6.0
Corn, pop, grain	0.10
Corn, pop, stover	6.0
Corn, sweet, forage	6.0
Corn, sweet, kernel plus cob with husks removed	0.10
Corn, sweet, stover	6.0
Cotton, gin byproducts	4.0
Cotton, undelinted seed	0.10
Cucumber	0.13
Egg	0.02
Grain, aspirated fractions	0.70
Goat, fat	0.02
Goat, kidney	0.20
Goat, liver	0.05
Goat, meat	0.02
Goat, meat byproducts, except kidney and liver	0.04
Grass, forage	10.0
Grass, hay	0.20
Horse, fat	0.02
Horse, kidney	0.20
Horse, liver	0.05
Horse, meat	0.02
Horse, meat byproducts, except kidney and liver	0.04
Leaf petioles, subgroup 4B	0.10
Melon, subgroup 9A	0.10
Milk	0.02
Okra	0.10
Onion, bulb, subgroup 3-07A	0.10
Onion, green, subgroup 3-07B	2.0
Peanut	0.20
Peanut, hay	20.0
Peanut, meal	0.40
Poultry, fat	0.02
Poultry, meat	0.02
Poultry, meat byproducts	0.05
Pumpkin	0.10

Commodity	Parts per million
Safflower, seed	0.10
Sesame, seed	0.13
Sheep, fat	0.02
Sheep, kidney	0.20
Sheep, liver	0.05
Sheep, meat	0.02
Sheep, meat byproducts, except kidney and liver	0.04
Sorghum, grain, forage	1.0
Sorghum, grain, grain	0.3
Sorghum, grain, stover	4.0
Sorghum, sweet, stalk	4.0
Soybean, forage	5.0
Soybean, hay	8.0
Soybean, seed	0.20
Spinach	0.50
Squash, winter	0.10
Sunflower, seed	0.50
Sunflower, meal	1.0
Tomato, paste	0.30
Turnip, greens	1.8
Vegetable, foliage of legume, except soybean,subgroup 7A	15.0
Vegetable, fruiting, group 8, except tabasco pepper	0.10
Vegetable, legume, group 6	0.30
Vegetable, root, except sugar beet, subgroup 1B, except carrot	0.30
Vegetable, tuberous and corm, subgroup 1C	0.20

40 CFR 180.368(a)(2) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: ***https://www.ecfr.gov***

▶ Hazardous Substances Data Bank (HSDB)

Tolerances with regional registration as defined in 180.1(l) are established for the combined residues (free and bound) of the herbicide metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity	Parts per million
Pepper, nonbell	0.50

40 CFR 180.368(c)(1) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: ***https://www.ecfr.gov***

▶ Hazardous Substances Data Bank (HSDB)

Tolerances with regional registration are established for residues of S-metolachlor, including its metabolites and degradates, in or on the commodities identified in the following table below. Compliance with the tolerance levels specified in the following table below is to be determined by measuring only the sum of free and bound S-metolachlor, S-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide, its R-

enantiomer, and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, calculated as the stoichiometric equivalent of S-metolachlor, in or on the commodity. /S-Metolachlor/

Commodity	Parts per million
Pepper, tabasco	0.50

40 CFR 180.368(c)(2) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: https://www.ecfr.gov

Hazardous Substances Data Bank (HSDB)

For more Allowable Tolerances (Complete) data for METOLACHLOR (6 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.6.4 Personal Protective Equipment (PPE)

In case of spill: Wear chemical safety glasses or goggles, rubber gloves, waterproof boots, and approved chemical cartridge respirator. In case of fire: Wear full protective clothing and self contained breathing apparatus. (USCG, 1999)

U.S. Coast Guard. 1999. Chemical Hazard Response Information System (CHRIS) - Hazardous Chemical Data. Commandant Instruction 16465.12C. Washington, D.C.: U.S. Government Printing Office.

CAMEO Chemicals

Applicators and other handlers must wear: Coveralls over short-sleeved shirt and short pants; Chemical-resistant gloves, such as barrier laminate or viton; Chemical-resistant footwear plus socks; Chemical-resistant headgear for overhead exposure; and Chemical-resistant apron when cleaning equipment, mixing or loading. /Me-Too-Lachlor Herbicide/

Drexel Chemical Company; Product Label for Me-Too-Lachlor Herbicide. Available from, as of March 22, 2012: https://www.drexchem.com/products/Labels/548SP-0310asterisk.pdf

Hazardous Substances Data Bank (HSDB)

Use this product only in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. /Me-Too-Lachlor Herbicide/

Drexel Chemical Company; Product Label for Me-Too-Lachlor Herbicide. Available from, as of March 22, 2012: https://www.drexchem.com/products/Labels/548SP-0310asterisk.pdf

Hazardous Substances Data Bank (HSDB)

Wear protective gloves and clothing to prevent any reasonable probability of skin contact. ... Contact lenses should not be worn when working with this chemical. Wear splash-proof chemical goggles and face shield unless full facepiece respiratory protection is worn. ... Provide emergency showers and eyewash.

Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 5th Edition Volume 1: A-H,Volume 2: I-Z. William Andrew, Norwich, NY 2008, p. 1761

Hazardous Substances Data Bank (HSDB)

Wear goggles or face shield when handling.

Weed Science Society of America. Herbicide Handbook. 5th ed. Champaign, Illinois: Weed Science Society of America, 1983., p. 313

Hazardous Substances Data Bank (HSDB)

12.6.5 Fire Prevention

NO open flames.

ILO International Chemical Safety Cards (ICSC)

12.6.6 Exposure Prevention

IN ALL CASES CONSULT A DOCTOR!

- ILO International Chemical Safety Cards (ICSC)

12.6.7 Inhalation Prevention

Use ventilation.

- ILO International Chemical Safety Cards (ICSC)

12.6.8 Skin Prevention

Protective gloves.

- ILO International Chemical Safety Cards (ICSC)

12.6.9 Eye Prevention

Wear safety goggles.

- ILO International Chemical Safety Cards (ICSC)

12.6.10 Ingestion Prevention

Do not eat, drink, or smoke during work. Wash hands before eating.

- ILO International Chemical Safety Cards (ICSC)

12.7 Stability and Reactivity

12.7.1 Air and Water Reactions

Slightly soluble in water. Hydrolyzed by strong mineral acids and strong alkalis.

- CAMEO Chemicals

12.7.2 Reactive Group

Amides and Imides

Halogenated Organic Compounds

Amines, Aromatic

- CAMEO Chemicals

12.7.3 Reactivity Profile

METOLACHLOR is a chlorinated acetamide. May react with azo and diazo compounds to generate toxic gases. May form flammable gases with strong reducing agents. Combustion generates mixed oxides of nitrogen (NOx).

▸ CAMEO Chemicals

12.7.4 Hazardous Reactivities and Incompatibilities

Oxidizers, strong acids, nitrates.

Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 5th Edition Volume 1: A-H,Volume 2: I-Z. William Andrew, Norwich, NY 2008, p. 1761

▸ Hazardous Substances Data Bank (HSDB)

12.8 Regulatory Information

12.8.1 Federal Drinking Water Guidelines

EPA 700 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

▸ Hazardous Substances Data Bank (HSDB)

12.8.2 State Drinking Water Guidelines

(FL) FLORIDA 110 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

▸ Hazardous Substances Data Bank (HSDB)

(MA) MASSACHUSETTS 100 ug/l

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

▸ Hazardous Substances Data Bank (HSDB)

(ME) MAINE 100 ug/l

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

▸ Hazardous Substances Data Bank (HSDB)

(MN) MINNESOTA 300 ug/L

USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present

▸ Hazardous Substances Data Bank (HSDB)

For more State Drinking Water Guidelines (Complete) data for METOLACHLOR (7 total), please visit the HSDB record page.

▸ Hazardous Substances Data Bank (HSDB)

12.8.3 FIFRA Requirements

Tolerances are established for the combined residues (free and bound) of the herbicide metolachlor, 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide, and its metabolites, determined as the derivatives, **2-[(2-ethyl-6-methylphenyl)amino]-1-propanol** and **4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone**, each expressed as the parent compound in the following raw agricultural commodities:

Commodity
Almond, hulls
Animal feed, nongrass, group 18
Cattle, fat
Cattle, kidney
Cattle, liver
Cattle, meat
Cattle, meat byproducts, except kidney and liver
Corn, field, forage
Corn, field, grain
Corn, field, stover
Corn, sweet, forage
Corn, sweet, kernel plus cob with husks removed
Corn, sweet, stover
Cotton, gin byproducts
Cotton, undelinted seed
Dillweed
Egg
Goat, fat
Goat, kidney
Goat, liver
Goat, meat
Goat, meat byproducts, except kidney and liver
Grass, forage
Grass, hay
Horse, fat
Horse, kidney
Horse, liver
Horse, meat
Horse, meat byproducts, except kidney and liver
Milk
Nut, tree, group 14
Okra
Peanut
Peanut, hay
Peanut, meal
Potato

Commodity
Poultry, fat
Poultry, meat
Poultry, meat byproducts
Safflower, seed
Sheep, fat
Sheep, kidney
Sheep, liver
Sheep, meat
Sheep, meat byproducts, except kidney and liver
Sorghum, grain, forage
Sorghum, grain, grain
Sorghum, grain, stover
Soybean, forage
Soybean, hay
Soybean, seed
Tomato
Vegetable, foliage of legume, subgroup 7A, except soybean
Vegetable, legume, group 6

40 CFR 180.368(a)(1) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: ***https://www.ecfr.gov***

▸ **Hazardous Substances Data Bank (HSDB)**

Tolerances are established for residues of **S-metolachlor**, including its metabolites and degradates, in or on the commodity(s), as defined. Compliance with the tolerance levels specified in the following table below is to be determined by measuring only the sum of free and bound **S-metolachlor**, S-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide, its R-enantiomer, and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and **4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone**, calculated as the stoichiometric equivalent of **S-metolachlor**, in or on the commodity. /**S-Metolachlor**/

Commodity
Aspaagus
Beet, sugar, molasses
Beet, sugar, roots
Beet, sugar, tops
Brassica, head and stem, subgroup 5A
Brassica, leafy greens, subgroup 5B
Bushberry subgroup 13-07B
Caneberry subgroup 13-07A
Carrot, roots
Cattle, fat
Cattle, kidney
Cattle, liver

Commodity
Cattle, meat
Cattle, meat byproducts, except kidney and liver
Corn, field, grain
Corn, field, forage
Corn, field, stover
Corn, pop, grain
Corn, pop, stover
Corn, sweet, forage
Corn, sweet, kernel plus cob with husks removed
Corn, sweet, stover
Cotton, gin byproducts
Cotton, undelinted seed
Cucumber
Egg
Grain, aspirated fractions
Goat, fat
Goat, kidney
Goat, liver
Goat, meat
Goat, meat byproducts, except kidney and liver
Grass, forage
Grass, hay
Horse, fat
Horse, kidney
Horse, liver
Horse, meat
Horse, meat byproducts, except kidney and liver
Leaf petioles, subgroup 4B
Melon, subgroup 9A
Milk
Okra
Onion, bulb, subgroup 3-07A
Onion, green, subgroup 3-07B
Peanut
Peanut, hay
Peanut, meal
Poultry, fat
Poultry, meat

Commodity
Poultry, meat byproducts
Pumpkin
Safflower, seed
Sesame, seed
Sheep, fat
Sheep, kidney
Sheep, liver
Sheep, meat
Sheep, meat byproducts, except kidney and liver
Sorghum, grain, forage
Sorghum, grain, grain
Sorghum, grain, stover
Sorghum, sweet, stalk
Soybean, forage
Soybean, hay
Soybean, seed
Spinach
Squash, winter
Sunflower, seed
Sunflower, meal
Tomato, paste
Turnip, greens
Vegetable, foliage of legume, except soybean,subgroup 7A
Vegetable, fruiting, group 8, except tabasco pepper
Vegetable, legume, group 6
Vegetable, root, except sugar beet, subgroup 1B, except carrot
Vegetable, tuberous and corm, subgroup 1C

40 CFR 180.368(a)(2) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: ***https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

Tolerances with regional registration as defined in 180.1(l) are established for the combined residues (free and bound) of the herbicide metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] and its metabolites, determined as the derivatives, 2-[2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound, in or on the following raw agricultural commodities:

Commodity
Pepper, nonbell

40 CFR 180.368(c)(1) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: ***https://www.ecfr.gov***

▸ Hazardous Substances Data Bank (HSDB)

Tolerances with regional registration are established for residues of S-metolachlor, including its metabolites and degradates, in or on the commodities identified in the following table below. Compliance with the tolerance levels specified in the following table below is to be determined by measuring only the sum of free and bound S-metolachlor, S-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide, its R-enantiomer, and its metabolites, determined as the derivatives, 2-(2-ethyl-6-methylphenyl)amino-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, calculated as the stoichiometric equivalent of S-metolachlor, in or on the commodity. /S-Metolachlor/

Commodity
Pepper, tabasco

40 CFR 180.368(c)(2) (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of December 20, 2011: https://www.ecfr.gov

Hazardous Substances Data Bank (HSDB)

For more FIFRA Requirements (Complete) data for METOLACHLOR (8 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

12.9 Other Safety Information

12.9.1 Toxic Combustion Products

... Poisonous gases including nitrogen oxides and chlorine are produced in fire. ...

Pohanish, R.P. (ed). Sittig's Handbook of Toxic and Hazardous Chemical Carcinogens 5th Edition Volume 1: A-H,Volume 2: I-Z. William Andrew, Norwich, NY 2008, p. 1761

Hazardous Substances Data Bank (HSDB)

12.9.2 Special Reports

USEPA/Office of Pesticide Programs; Reregistration Eligibility Decision Document - Metolachlor, EPA 738-R-95-006 (April 1995). The RED summarizes the risk assessment conclusions and outlines any risk reduction measures necessary for the pesticide to continue to be registered in the U.S.[Available from, as of January 31, 2012: http://www.epa.gov/pesticides/reregistration/status.htm]

Hazardous Substances Data Bank (HSDB)

13 Toxicity

13.1 Toxicological Information

13.1.1 Toxicity Summary

Metolachlor acts by inhibition of elongases and of the **geranylgeranyl pyrophosphate** (**GGPP**) cyclases, which are part of the gibberellin pathway. It also binds to nAChRs in nervous systems and causes endocrine disruption in humans by binding to and inhibiting the estrogen receptor. (T10, L913, A590)

- **Toxin and Toxin Target Database (T3DB)**

13.1.2 NIOSH Toxicity Data

- **The National Institute for Occupational Safety and Health (NIOSH)**

13.1.3 Evidence for Carcinogenicity

Cancer Classification: Group C Possible Human Carcinogen

USEPA Office of Pesticide Programs, Health Effects Division, Science Information Management Branch: "Chemicals Evaluated for Carcinogenic Potential" (April 2006)

- **Hazardous Substances Data Bank (HSDB)**

CLASSIFICATION: C; possible human carcinogen. BASIS FOR CLASSIFICATION: Classification is based on the appearance of proliferative liver lesions (combined neoplastic nodules and carcinomas) at highest dose tested (3000 ppm) in female rats. HUMAN CARCINOGENICITY DATA: None. ANIMAL CARCINOGENICITY DATA: Limited.

U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS). Summary on Metolachlor (51218-45-2). Available from, as of March 15, 2000: ***https://www.epa.gov/iris/***

- **Hazardous Substances Data Bank (HSDB)**

13.1.4 Carcinogen Classification

Carcinogen Classification	No indication of carcinogenicity to humans (not listed by IARC).

Toxin and Toxin Target Database (T3DB)

13.1.5 Health Effects

Health effects of metolachlor include CNS depression, dizziness, dyspnea, liver damage, nephritis, cardiovascular failure, and adverse reproductive effects. (A571)

Toxin and Toxin Target Database (T3DB)

13.1.6 Exposure Routes

The substance can be absorbed into the body by inhalation of its aerosol.

ILO International Chemical Safety Cards (ICSC)

Inhalation (L914) ; oral (L914) ; dermal (L914) ; eye contact (L914).

Toxin and Toxin Target Database (T3DB)

13.1.7 Symptoms

Signs of human intoxication from metolachlor and/or its formulations (presumably following acute deliberate or accidental exposures) include abdominal cramps, anemia, ataxia, dark urine, methemoglobinemia, cyanosis, hypothermia, collapse, convulsions, diarrhea, GI irritation, jaundice, weakness, nausea, shock, sweating, vomiting, skin irritation, dermatitis, sensitization dermatitis, eye and mucous membrane irritation, and corneal opacity. (A571)

Toxin and Toxin Target Database (T3DB)

13.1.8 Inhalation Symptoms

Headache. Nausea.

ILO International Chemical Safety Cards (ICSC)

13.1.9 Ingestion Symptoms

Abdominal cramps.

ILO International Chemical Safety Cards (ICSC)

13.1.10 Acute Toxicity Link

Chemical: METOLACHLOR

USGS Columbia Environmental Research Center

13.1.11 Adverse Effects

Methemoglobinemia - The presence of increased methemoglobin in the blood; the compound is classified as secondary toxic effect

Skin Sensitizer - An agent that can induce an allergic reaction in the skin.

Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

13.1.12 Acute Effects

ChemIDplus

13.1.13 Toxicity Data

LD50: 1200-2780 mg/kg (Oral, Oral) (L914) LD50: > 2000 mg/kg (Dermal, Rat) (L914) LC50: > 4.3 mg/L/4hr (L914)

Toxin and Toxin Target Database (T3DB)

13.1.14 Treatment

Consider gastric lavage, as well was dilution with milk or water after ingestion. Administer charcoal as a slurry following ingestion; however, activated charcoal should not be given to patients ingesting strong acidic or basic caustic chemicals. In case of inhalation, move patient to fresh air. Monitor for respiratory distress. If cough or difficulty breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer oxygen and assist ventilation as required. Treat bronchospasm with inhaled beta2 agonist and oral or parenteral corticosteroids. Irrigate exposed eyes with copious amounts of room temperature water for at least 15 minutes. Following dermal exposure, remove contaminated clothing and wash exposed area thoroughly with soap and water. Treat dermal irritation or burns with standard topical therapy. Patients developing dermal hypersensitivity reactions may require treatment with systemic or topical corticosteroids or antihistamines. Administer symptomatic treatment as necessary. (T36)

Toxin and Toxin Target Database (T3DB)

13.1.15 Interactions

The reproductive toxicity of a mixture of 5 pesticides (alachlor, atrazine, cyanazin, metolachlor, and metribuzin) and one fertilizer (ammonium nitrate) was evaluated in Swiss mice using the continuous breeding protocol. These chemicals and their relative concn in the stock mixture were selected on the basis of groundwater survey data from Iowa. Mice received the mixture in the drinking water at 0X, 1X, 10X and 100X, where 1X was the median concn of each component as determined by the surveys. F0 mice were fertile throughout 18 weeks exposure. mixture did not adversely affect reproductive competence, F0 body weight, food or water consumption, organ weights, or sperm parameters at necropsy. No treatment related clinical signs were noted. F1 preweaning growth and maturation were unaffected by mixture. No treatment related clinical signs or adverse effect of mixture on F1 reproductive competence, food and water consumption, male or female body weight, or selected male and female organ weights, sperm parameters, vaginal cytology, or histology of selected organs was observed. In summary, exposure to mixture in the drinking water at dose levels as high as 100X the median concn of the components in contaminated groundwater did not cause clearcut generalized or reproductive toxicity in either the F0 or F1 generation of Swiss mice.

George JD et al; Toxicologist 13 (1): 77 (1993)

Hazardous Substances Data Bank (HSDB)

Male Fischer 344 rats and female B6C3F1 mice were each exposed through their drinking **water** to a mixture of pesticides and **ammonium nitrate** that simulated contaminated groundwater in California (California Chemical Mixture). Exposures were for 71 or 91 days, respectively. In addition, B6C3F1 female mice were exposed for 91 days to another pesticide and **ammonium nitrate** mixture (Iowa Chemical Mixture) through their drinking **water**. The spleen were removed from the animals, and the splenocytes were cultured for analyses of sister chromatid exchange, chromosome aberrations, and micronuclei in **cytochalasin B** induced binucleate cells. A concn related increase in sister chromatid exchanges was found in the splenocytes of the rat at the 1X, 10X and 100X levels of the California Chemical Mixture and at the 100X concn of the California Chemical Mixture in the mouse. There were no other consistent cytogenetic effects observed with the California Chemical Mixture, and no statistically significant cytogenetic damage was observed in mice exposed to the Iowa Chemical Mixture. Evidence from the literature is discussed in order to infer which chemical or chemicals in the California Chemical Mixture might be responsible for the observed sister chromatid exchange response.

PMID:7685493
Kligerman AD et al; Mutat Res 300 (2): 125-34 (1993)

Hazardous Substances Data Bank (HSDB)

13.1.16 Antidote and Emergency Treatment

There is no specific antidote to counteract the toxic affects of metolachlor ... Laboratory studies have shown that metolachlor has a high affinity for activated **charcoal**. Therefore, if ingestion is less than 10 mg/kg body wt, it is probably best treated by administering 30-50 gm of activated **charcoal** in 3-4 oz of **water**.

Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 3. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 1345

Hazardous Substances Data Bank (HSDB)

/SRP:/ Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing **water**. Do not induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention. /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160

Hazardous Substances Data Bank (HSDB)

/SRP:/ Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer **oxygen** by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with **water**. Irrigate each eye continuously with 0.9% saline (NS) during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of **water** for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160

Hazardous Substances Data Bank (HSDB)

/SRP:/ Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag valve mask device may be beneficial. Consider drug therapy for pulmonary edema ... . Consider administering a beta agonist such as **albuterol** for severe bronchospasm ... . Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start IV administration of D5W /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with **diazepam** or **lorazepam** ... . Use **proparacaine hydrochloride** to assist eye irrigation ... . /Poisons A and B/

Currance, P.L. Clements, B., Bronstein, A.C. (Eds).; Emergency Care For Hazardous Materials Exposure. 3Rd edition, Elsevier Mosby, St. Louis, MO 2005, p. 160-1

Hazardous Substances Data Bank (HSDB)

13.1.17 Human Toxicity Excerpts

/SIGNS AND SYMPTOMS/ Signs of human intoxication from metolachlor and/or its formulations (presumably following acute deliberate or accidental exposures) include abdominal cramps, anemia, ataxia, dark urine, methemoglobinemia, cyanosis, hypothermia, collapse, convulsions, diarrhea, GI irritation, jaundice, weakness, nausea, shock, sweating, vomiting, CNS depression, dizziness, dyspnea, liver damage, nephritis, cardiovascular failure, skin irritation, dermatitis, sensitization dermatitis, eye and mucous membrane irritation, corneal opacity and adverse reproductive effects.

USEPA; Health Advisories for 50 Pesticides p.618 (1988) NTIS PB88-245931

Hazardous Substances Data Bank (HSDB)

13.1.18 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Beagle dogs fed 0, 100, 300, or 1000 ppm /metolachlor/ for six months displayed a NOEL of 300 ppm (equivalent to 7.5 mg/kg/day) (MRID 00032174). The LOEL was 1000 ppm (equivalent to 25 mg/kg/day) based upon reduced body weight gains and food consumption in the high dose dogs.

USEPA/Office of Pesticide Programs; Reregistration Eligibility Decision (RED)- Metolachlor p. 9. EPA 738-R-95-006 (April 1995). Available from, as of February 3, 2012: https://www.epa.gov/pesticides/reregistration/status.htm

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ In a three-month feeding study in beagle dogs displayed no effects at the doses of 500 and 1000 ppm /metolachlor/, the NOEL for toxicity was equal to or greater than 1000 ppm (equivalent to 25 mg/kg/day) (guideline 82-1; MRID No. 00017690).

USEPA/Office of Pesticide Programs; Reregistration Eligibility Decision (RED)- Metolachlor p. 9. EPA 738-R-95-006 (April 1995). Available from, as of February 3, 2012: https://www.epa.gov/pesticides/reregistration/status.htm

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ A 21-day dermal toxicity study was performed on New Zealand white rabbits with 0, 10, 100, or 1000 mg/kg/day of metolachlor ... . The systemic NOEL was 100 mg/kg/day for both sexes. The systemic LOELs was 1000 mg/kg/day based upon increased **bilirubin** in both sexes, increased relative and absolute liver weights in males and increased kidney weights in females.

USEPA/Office of Pesticide Programs; Reregistration Eligibility Decision (RED)- Metolachlor p. 9. EPA 738-R-95-006 (April 1995). Available from, as of February 3, 2012: https://www.epa.gov/pesticides/reregistration/status.htm

Hazardous Substances Data Bank (HSDB)

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ In the subchronic dog study, no effects were observed in dogs at the high dose of approximately 70 mg/kg/day /**s-metolachlor**/. /**s-metolachlor**/

USEPA; s-Metolachlor: s-Metolachlor Aggregate Human Health Risk Assessment. Document ID: EPA-HQ-OPP-2006-0292 p. 16 (July 13, 2006). Available from, as of February 3, 2012: https://www.regulations.gov/#!home

Hazardous Substances Data Bank (HSDB)

For more Non-Human Toxicity Excerpts (Complete) data for METOLACHLOR (19 total), please visit the **HSDB record page**.

Hazardous Substances Data Bank (HSDB)

13.1.19 Non-Human Toxicity Values

LC50 Rat inhalation >2.02 mg/L/4 hr air

MacBean C, ed.Metolachlor (51218-45-2). In: The e-Pesticide Manual, 15th Edition, Version 5.0.1 (2010). Surrey UK, British Crop Protection Council.

Hazardous Substances Data Bank (HSDB)

LD50 Rabbit dermal >2000 mg/kg bw

European Chemicals Bureau; IUCLID Dataset for Metolachlor (51218-45-2), p.26 (2000 CD-ROM edition). Available from, as of February 2, 2012: https://ecb.jrc.ec.europa.eu/esis/

Hazardous Substances Data Bank (HSDB)

LD50 Rat dermal 3170 mg/kg bw

European Chemicals Bureau; IUCLID Dataset for Metolachlor (51218-45-2), p.26 (2000 CD-ROM edition). Available from, as of February 2, 2012: https://ecb.jrc.ec.europa.eu/esis/

Hazardous Substances Data Bank (HSDB)

LC50 Rat inhalation >4.33 mg/L/4 hr

European Chemicals Bureau; IUCLID Dataset for Metolachlor (51218-45-2), p.26 (2000 CD-ROM edition). Available from, as of February 2, 2012: https://ecb.jrc.ec.europa.eu/esis/

Hazardous Substances Data Bank (HSDB)

For more Non-Human Toxicity Values (Complete) data for METOLACHLOR (12 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

13.1.20 Ecotoxicity Values

LC50; Species: Anas platyrhynchos (Mallard Duck) age 14 days; dietary >10000 ppm for 8 days

USEPA/OPP, EFED; Pesticide Ecotoxicity Database (2000) as cited in the ECOTOX database. Available from, as of February 8, 2012: https://cfpub.epa.gov/ecotox/

Hazardous Substances Data Bank (HSDB)

LC50; Species: Anas platyrhynchos (Mallard Duck) age 10 days; dietary >5620 ppm for 8 days /S-Metolachlor/

USEPA/OPP, EFED; Pesticide Ecotoxicity Database (2000) as cited in the ECOTOX database. Available from, as of August 28, 2012: https://cfpub.epa.gov/ecotox/

Hazardous Substances Data Bank (HSDB)

LD50; Species: Anas platyrhynchos (Mallard Duck) age 14 days; oral via capsule 4640 mg/kg (95% confidence interval: 3000-7200 mg/kg)

USEPA/OPP, EFED; Pesticide Ecotoxicity Database (2000) as cited in the ECOTOX database. Available from, as of February 8, 2012: https://cfpub.epa.gov/ecotox/

Hazardous Substances Data Bank (HSDB)

LD50; Species: Anas platyrhynchos (Mallard Duck) age 16 wk; oral via capsule >2510 mg/kg /S-Metolachlor/

USEPA/OPP, EFED; Pesticide Ecotoxicity Database (2000) as cited in the ECOTOX database. Available from, as of August 28, 2012: https://cfpub.epa.gov/ecotox/

Hazardous Substances Data Bank (HSDB)

For more Ecotoxicity Values (Complete) data for METOLACHLOR (58 total), please visit the HSDB record page.

Hazardous Substances Data Bank (HSDB)

13.1.21 Ecotoxicity Excerpts

/BIRDS and MAMMALS/ ...Studies indicate metolachlor has chronic reproductive effects on birds and mammals at the highest tested dose. These effects, noted for both groups of organisms at approximately 1000 mg/kg diet, include a reduction in the number of eggs (birds) and reduced weight of pups (rats). No treatment-related mortality or other effects were noted in the studies.

USEPA/Office of Pesticide Programs; Risks of Metolachlor Use to Federally Threatened California Red-legged Frog (Rana aurora draytonii). p.58 Identification Number: EPA-HQ-OPP-2009-0081-0068 (July 2007). Available from, as of March 26, 2012: https://www.regulations.gov/#!home

Hazardous Substances Data Bank (HSDB)

/AQUATIC SPECIES/ /Researchers/ examined the toxicity mitigation efficiency of a hydrologically modified backwater wetland amended with a pesticide mixture of atrazine, metolachlor, and fipronil, using 96 hr survival bioassays with Hyalella azteca /scud/. Significant H. azteca 96 hr mortality occurred within the first 2 hr of amendment at the upstream amendment site but not at any time at the downstream site. H. azteca survival varied spatially and temporally in conjunction with measured pesticide mixture concentrations. Hyalella azteca 96 hr survival pesticide mixture effects concentrations ranges were 10.214-11.997, 5.822-6.658, 0.650-0.817, and 0.030-0.048 ug/L for atrazine, metolachlor, fipronil, and fipronil-sulfone, respectively.

PMID:19701594

Lizotte RE Jr et al; Bull Environ Contam Toxicol 83 (6): 836-40 (2009)

Hazardous Substances Data Bank (HSDB)

/AQUATIC SPECIES/ The toxicities of two herbicides (alachlor and metolachlor) and an organophosphate insecticide (chlorpyrifos) were evaluated individually and with either herbicide in binary mixture with chlorpyrifos in fourth-instar larvae of the aquatic midge (Chironomus tentans). Alachlor alone up to 1,000 ug/L did not exhibit significant toxicity, whereas metolachlor at 1,000 ug/L affected 58% of midges in 72 hr bioassays. However, alachlor at 1,000 ug/L and metolachlor at 10, 100, and 1,000 ug/L enhanced the toxicity of chlorpyrifos to the midges. Furthermore, alachlor and metolachlor at 1,000 ug/L reduced acetylcholinesterase (AChE) activity by 34.3% and 27.6%, respectively, in the treated midges. Although alachlor at 1,000 ug/L did not significantly affect protein production in the treated midges, it reduced glutathione S-transferases (GST) total activities by 1.9 to 2.1 fold. In contrast, metolachlor at 1,000 ug/L reduced protein production by 3.2 fold, which was associated with a 2.8 fold reduction of cytochrome P450 O-deethylation total activity and 1.4 to 1.7 fold reductions of GST total activities in the treated midges. Such reduced total activities of the major detoxification enzymes in herbicide-treated midges might impede the metabolic detoxification of chlorpyrifos and, therefore, increase the susceptibility of the midges to chlorpyrifos.

PMID:18026775
Jin-Clark Y et al; Arch Environ Contam Toxicol. 54 (4): 645-52 (2008)

▶ Hazardous Substances Data Bank (HSDB)

/AQUATIC SPECIES/ The toxicity of the chiral herbicides rac-metolachlor and S-metolachlor to Chlorella pyrenoidosa /green algae/ was determined and compared in this study, based on four different test endpoints: the growth inhibition rate, the chlorophyll a and chlorophyll b concentration, the catalase activity, and the ultrastructural morphology of cells. The 24, 48, 72, and 96 hr EC50 values of rac-metolachlor were 0.196, 0.241, 0.177 and 0.152 mg/L, respectively; these values were higher than those of S-metolachlor, which were 0.116, 0.106, 0.081 and 0.068 mg/L, respectively. This indicates that S-metolachlor was more toxic to C. pyrenoidosa than rac-metolachlor. The Chla and Chlb concentration of C. pyrenoidosa treated by rac-metolachlor was higher than that treated by S-metolachlor. In general, the catalase activity of C. pyrenoidosa treated by S-metolachlor was higher than that exposed to rac-metolachlor, and catalase activity was inhibited at high concentrations of both herbicides. The ultrastructural morphology of cells grown in the two herbicides was observed by transmission electron microscopy. The cell wall separated from the cell membrane, accumulated starch granules were observed in the chloroplast, and some lipid droplets and unknown electron-opaque deposits were also observed in the cytoplasm.

PMID:19428127
Liu H, Xiong M; Aquat Toxicol 93 (2-3): 100-6 (2009)

▶ Hazardous Substances Data Bank (HSDB)

For more Ecotoxicity Excerpts (Complete) data for METOLACHLOR (16 total), please visit the HSDB record page.

▶ Hazardous Substances Data Bank (HSDB)

13.1.22 National Toxicology Program Studies

This study was conducted to assess the potential for a mixture of 5 pesticides (alachlor, atratine, cyanazin, metolachlor, and metribuzin) and one fertilizer component, ammonium nitrate (Iowa Pesticide/Fertilizer mixture, IOWA) administered in the drinking water at specified levels to cause developmental toxicity. IOWA was administered in the drinking water to timed-pregnant Sprague-Dawley (CD) rats (26-29 per group) on gestational days (gd) 6 to 20 at dose levels of IX, I0X, and I00X in reagent grade water containing 512 ppm propylene glycol, where X was the median concentration of the components observed in groundwater determination in IOWA. A vehicle control formulation containing 512 ppm propylene glycol in reagent grade water and blank reagent grade drinking water were also administered to two additional groups. Estimated mean exposure to the components of the mixture was 96-102% of the target dose for each dose level based on the median result of the analysis of marker compounds metribuzin and ammonium nitrate. Animals were observed daily for clinical signs of toxicity. Food and water consumption and body weights were determined on gd 0, 3, 6, 9, 12, 15, 18, and 20. All animals were killed on gd 20 and examined for maternal body weight, implant status, fetal weight, sex, and morphological development including external, visceral, and skeletal development. IOWA-exposed females did not exhibit any significant treatment-related clinical signs of toxicity. Maternal food consumption did not differ significantly between the water and vehicle control groups and was not consistently altered by IOWA treatment in a dose-related manner. Maternal water consumption tended to be higher in the vehicle control group than in the water control group, but there was little difference between the vehicle control group and the IOWA-treated groups. Maternal body weights were unaffected by treatment. Maternal liver weight (absolute and relative) was slightly higher in the vehicle control group compared to the water control group, consistent with exposure to the propylene glyco1 in the vehicle control formulation. However, there was no difference in the maternal liver weight between the vehicle control and the IOWA-treated groups. Thus, I00X IOWA was the maternal no-observed-adverse-effect level (NOAEL) in this study. Gravid uterine weight was unaffected by exposure to IOWA. In addition, there was no effect of treatment on prenatal development or fetal body weight. IOWA exposure did not alter the incidence of fetal malformations or variations. Thus, I00X IOWA was the developmental NOAEL.

DHHS/NTP; Toxicology and Carcinogenesis Studies of TOX-36 Pesticide/fertilizer contamination--mixture 3 (51218-45-2 is part of Mixture) (PESTFERTMIX3) (1993) Technical Rpt Series No. C89010. Available from, as of February 2, 2012: https://ntp-server.niehs.nih.gov/

▶ Hazardous Substances Data Bank (HSDB)

The California (aldicarb, atrazine, 1,2-dibromo-3-chloropropane, 1,2- dichloropropane, ethylene dibromide, simazine, and ammonium nitrate) and Iowa (alachlor, atrazine, cyanazine, metolachlor, metribuzin, and ammonium nitrate) pesticide mixtures were tested for induction of micronuclei in peripheral blood erythrocytes of female mice. Results of tests with the California mixture were negative. Significant increases in micronucleated normochromatic erythrocytes were seen at the two-highest concentrations (10X and 100X) of the Iowa mixture, but the increases were within the normal range of micronuclei in historical control animals.

Splenocytes of male rats and female mice exposed to these mixtures were examined for micronucleus and sister chromatid exchange frequencies. Sister chromatid exchange frequencies were marginally increased in rats and mice receiving the California mixture, but neither species exhibited increased frequencies of micronucleated splenocytes. None of these changes were considered to have biological importance.

DHHS/NTP; Toxicology and Carcinogenesis Studies of TOX-36 Pesticide/fertilizer contamination--mixture 3 (51218-45-2 is part of Mixture) (PESTFERTMIX3) (1993) Technical Rpt Series No. C89010. Available from, as of February 2, 2012: ***https://ntp-server.niehs.nih.gov/***

▸ Hazardous Substances Data Bank (HSDB)

Toxicity studies were performed with pesticide and fertilizer mixtures representative of groundwater contamination found in California and Iowa. The California mixture was composed of **aldicarb**, **atrazine**, **1,2-dibromo-3-chloropropane**, **1,2- dichloropropane**, **ethylene dibromide**, **simazine**, and **ammonium nitrate**. The Iowa mixture contained **alachlor**, **atrazine**, **cyanazine**, metolachlor, **metribuzin**, and **ammonium nitrate**. The mixtures were administered in drinking **water** (with 512 ppm **propylene glycol**) to ... B6C3F1 mice of each sex at concentrations ranging from 0.1X to 100X, where 1X represented the median concentrations of the individual chemicals found in studies of groundwater contamination from normal agricultural activities. ... In 26-week drinking **water** studies in mice, one male receiving the California mixture at 100X died during the study, and one control female and one female in the 100X group in the Iowa mixture study also died early. It could not be determined if the death of either of the mice in the 100X groups was related to consumption of the pesticide/fertilizer mixtures. **Water** consumption and body weight gains were not affected in these studies, and no signs of toxicity were noted in clinical observations or in neurobehavioral assessments. No clear adverse effects were noted in clinical pathology, reproductive system, organ weight, or histopathologic evaluations of exposed mice.

DHHS/NTP; Toxicology and Carcinogenesis Studies of TOX-36 Pesticide/fertilizer contamination--mixture 3 (51218-45-2 is part of Mixture) (PESTFERTMIX3) (1993) Technical Rpt Series No. C89010. Available from, as of February 2, 2012: ***https://ntp-server.niehs.nih.gov/***

▸ Hazardous Substances Data Bank (HSDB)

Toxicity studies were performed with pesticide and fertilizer mixtures representative of groundwater contamination found in California and Iowa. The California mixture was composed of **aldicarb**, **atrazine**, **1,2-dibromo-3-chloropropane**, **1,2- dichloropropane**, **ethylene dibromide**, **simazine**, and **ammonium nitrate**. The Iowa mixture contained **alachlor**, **atrazine**, **cyanazine**, metolachlor, **metribuzin**, and **ammonium nitrate**. The mixtures were administered in drinking **water** (with 512 ppm **propylene glycol**) to F344/N rats ... of each sex at concentrations ranging from 0.1X to 100X, where 1X represented the median concentrations of the individual chemicals found in studies of groundwater contamination from normal agricultural activities. ... In 26-week drinking **water** studies of the California and the Iowa mixtures, all rats (10 per sex and group) survived to the end of the studies, and there were no significant effects on body weight gains. **Water** consumption was not affected by the pesticide/fertilizer contaminants, and there were no clinical signs of toxicity or neurobehavioral effects as measured by a functional observational battery, motor activity evaluations, thermal sensitivity evaluations, and startle response. There were no clear adverse effects noted in clinical pathology (including serum cholinesterase activity), organ weight, reproductive system, or histopathologic evaluations, although absolute and relative liver weights were marginally increased with increasing exposure concentration in both male and female rats consuming the Iowa mixture.

DHHS/NTP; Toxicology and Carcinogenesis Studies of TOX-36 Pesticide/fertilizer contamination--mixture 3 (51218-45-2 is part of Mixture) (PESTFERTMIX3) (1993) Technical Rpt Series No. C89010. Available from, as of February 2, 2012: ***https://ntp-server.niehs.nih.gov/***

▸ Hazardous Substances Data Bank (HSDB)

13.2 Ecological Information

13.2.1 EPA Ecotoxicity

Pesticide Ecotoxicity Data from EPA

EPA Pesticide Ecotoxicity Database

13.2.2 US EPA Regional Screening Levels for Chemical Contaminants

Resident Soil (mg/kg)	9.50e+02
Industrial Soil (mg/kg)	1.20e+04
Tapwater (ug/L)	2.70e+02
Risk-based SSL (mg/kg)	3.20e-01
Chronic Oral Reference Dose (mg/kg-day)	1.50e-01
Fraction of Contaminant Absorbed in Gastrointestinal Tract	1
Fraction of Contaminant Absorbed Dermally from Soil	0.1

EPA Regional Screening Levels for Chemical Contaminants at Superfund Sites

13.2.3 US EPA Regional Removal Management Levels for Chemical Contaminants

Resident Soil (mg/kg)	9.50e+03
Industrial Soil (mg/kg)	1.20e+05
Tapwater (ug/L)	2.70e+03
Chronic Oral Reference Dose (mg/kg-day)	1.50e-01
Fraction of Contaminant Absorbed in Gastrointestinal Tract	1
Fraction of Contaminant Absorbed Dermally from Soil	0.1

EPA Regional Screening Levels for Chemical Contaminants at Superfund Sites

13.2.4 ICSC Environmental Data

The substance is toxic to aquatic organisms. Avoid release to the environment in circumstances different to normal use.

ILO International Chemical Safety Cards (ICSC)

13.2.5 Environmental Fate/Exposure Summary

Metolachlor's production may result in its release to the environment through various waste streams; its use as a herbicide will result in its direct release to the environment. If released to air, a vapor pressure of 3.14X10-5 mm Hg at 25 °C indicates metolachlor will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase metolachlor will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 7 hours. Particulate-phase metolachlor will be removed from the atmosphere by wet or dry deposition. Metolachlor is expected to be susceptible to

direct photolysis by sunlight with reported half-lives of 8-22 days. If released to soil, metolachlor is expected to have very high to slight mobility based upon a Koc range of 22-2320. Volatilization from moist soil surfaces is not expected to be an important fate process based upon a Henry's Law constant of 9.0X10-9 atm-cu m/mole; however, volatilization has been shown to occur at elevated temperatures. Metolachlor was not biodegraded in contaminated soil after 160 days of incubation, indicating that biodegradation is not an importanat environmental fate process in soil. Some loss of metolachlor from soil surfaces will occur as a result of photolysis by sunlight. If released into water, metolachlor is expected to adsorb to suspended solids and sediment based upon the Koc range. The aquatic biodegradation half-lives for metolachlor under aerobic and anaerobic conditions are 47 and 78 days, respectively. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's Henry's Law constant. The photolysis half-life of metolachlor in lake water under summer conditions was reported as 11 days; however humic substances retarded the photolysis rate. The estimated hydrolysis half-life of metolachlor in water is 210 days. Whole body BCFs of <1 and 69 suggest bioconcentration in aquatic organisms is low to moderate. Occupational exposure to metolachlor may occur through inhalation and dermal contact with this compound at workplaces where metolachlor is produced or used. Monitoring data indicate that the general population may be exposed to metolachlor via inhalation of ambient air, and ingestion of contaminated food and drinking water. (SRC)

▸ Hazardous Substances Data Bank (HSDB)

13.2.6 Artificial Pollution Sources

Metolachlor's production may result in its release to the environment through various waste streams; its use as a herbicide(1) will result in its direct release to the environment(SRC).

(1) MacBean C, ed; e-Pesticide Manual. 15th ed., ver. 5.1, Alton, UK; British Crop Protection Council. Metolachlor (51218-45-2) (2008-2010)

▸ Hazardous Substances Data Bank (HSDB)

13.2.7 Environmental Fate

TERRESTRIAL FATE: Based on a classification scheme(1), a range of Koc values from 22 to 2320(2-4) indicates that metolachlor is expected to have very high to slight mobility in soil(SRC). Volatilization was shown to be affected by residue cover, spatial concentration on the surface and timing of precipitation; cumulative volatilization loss of 22% and 6% applied using broadcast treatment and banded treatment, respectively, was noted during a 10 day field study(5). However, volatilization from moist soil surfaces is not expected to be an important fate process(SRC) given a Henry's Law constant of 9.0X10-9 atm-cu m/mole(6). Metolachlor is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 3.14X10-5 mm Hg(7). Some loss of metolachlor from soil surfaces will occur as a result of photolysis by sunlight(6). Metolachlor was not biodegraded in contaminated soil after 160 days of incubation(8), indicating that biodegradation is not an importanat environmental fate process in soil(SRC).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Laabs V, Amelung W; J Agric Food Chem 53: 7184-92 (2005) (3) Ahrens W; Herbicide Handbook of the Weed Science Society of America. 7th ed Champaign, IL: Weed Science Society of America p. 199 (1994) (4) Krutz JL et al; J Environ Qual 33: 939-45 (2004) (5) Prueger JH et al; J Environ Qual 28: 75-81 (1999) (6) Chesters G et al; Environ Contam Toxicol 110: 1-74 (1989) (7) Wauchope RD et al; Rev Environ Contam Toxicol 123: 1-155 (1992) (8) Anhalt JC et al; J Environ Sci Health: B35: 417-38 (2000)

▸ Hazardous Substances Data Bank (HSDB)

TERRESTRIAL FATE: Degradation half-lives of metolachlor simulated under varying laboratory conditions. Observed field degradation half-lives of metolachlor in loamy soil (42% sand, 24% clay, 34% silt, 1.7% organic matter) were 17.7, 28.8 and 17.2 days in 1993, 1994 and 1996, respectively(1).

Temperature (deg C)	Moisture (%)	Half-life (days)
35	100	5.7
35	70	7.3
35	40	11.3
25	100	8.6
25	70	10.2
25	40	15.2
20	100	12.2
15	100	18.0
15	70	21.4
15	40	27.4
10	100	47.5
5	100	100.7

(1) Dinelli G et al; J Agric Food Chem 48: 3037-43 (2000)

Hazardous Substances Data Bank (HSDB)

TERRESTRIAL FATE: Degradation half-lives of metolachlor were 14 and 7 days in Sungai Buluh (organic carbon 2%, clay 10%, silt 3.7%, sand 86.3%, pH 4.8) and Holyrood (organic carbon 1%, clay 21.1%, silt 4.1%, sand 74.8%, pH 4.6) series soils under simulated natural conditions(1). Degradation of metolachlor was studied in an aqueous/sediment environment for 112 days using Bojac sandy loam collected from the eastern shore of Virginia(2). The degradation rate constant and half-life of metolachlor in the sediment were 0.008/day and 34 days, respectively, the values in the water layer were 0.012/day and 8 days, respectively(2). Degradation rate constants and half-lives in soil without switchgrass were 0.52/day and 9.6 days, respectively, in soil with switchgrass values were 0.53/day and 6.0 days, respectively(2). [14C]Metolachlor was studied in a fresh water-sediment temperature-controlled greenhouse at 25 °C with a 14:10 hour light:dark photoperiod(3). The distribution of [14C]metolachlor was 23.7% in water, 6.6% in sediment and [14C]metolachlor extractable degradates, including carbinol and morpholinone, were 37.4% in water and 5.2% in sediment after 16 days of incubation(3). After 60 days of incubation the distribution of [14C]metolachlor was 0.7% in water, 0.6% in sediment and [14C]metolachlor extractable degradates were 60.6% in water and 9.2% in sediment(3). Degradation rate constants for metolachlor in three fields in eastern Colorado were 0.037 to 0.039/day with corresponding half-lives of 18.8 to 17.9 days, experiments were conducted from 2003 to 2005(4). The dissipation of metolachlor was detected following 3 applications to a clay loam soil at the Animal Research Center Farm, Ottawa between 1987 and 1990(5). Residue decline, leachability into the soil profile, movement into tile drainage water, and contamination of the groundwater of metolachlor were measured; and the amount of the herbicide applied to the soil surface was accounted for in the upper layer during the first week following treatment. The decline of metolachlor was followed in the upper 15 cm of the soil for 332, 364, and 370 days respectively in 1987, 1988 and 1989 and the half-lives of 80, 99, and 142 days were calculated. Metolachlor was present in groundwaters 1.2 to 4.6 m deep between the fall of 1988 to the summer of 1989. It was estimated that by the end of the season between 0.06 and 0.19% of the metolachlor moved into the shallow groundwater between the depths of 1.2 and 4.6 m(5).

(1) Ismail BS, Quirinus L; Bull Environ Contam Toxicol 65: 530-6 (2000) (2) Mersie W et al; Environ Toxicol Chem 23: 2627-32 (2004) (3) Rice PH et al; Environ Toxicol Chem 23: 1145-55 (2004) (4) Shaner DL, Henry WB; J Environ Qual 36: 128-34 (2007) (5) Frank R et al; Arch Environ Contam Toxicol 21: 253-62 (1991)

Hazardous Substances Data Bank (HSDB)

AQUATIC FATE: Based on a classification scheme(1), a range of Koc values from 22 to 2320(2-4) indicate that metolachlor is expected to adsorb to suspended solids and sediment(SRC). Volatilization from water surfaces is not expected(5) based upon a Henry's Law constant of 9.0X10-9 atm-cu m/mole(6). When an aqueous solution of metolachlor was irradiated with natural sunlight, only 8% of the metolachlor photodecomposed in 30 days(6). However, the photolysis half-life of metolachlor in lake water under summer conditions was reported as 11 days(7). Humic substances retarded the photolysis of metolachlor in water(8). The estimated hydrolysis half-life of metolachlor in water is 210 days(9). According to a classification scheme(10), whole body BCFs of <1(11) and 99(6) suggest the potential for bioconcentration in aquatic organisms is low to moderate(SRC). The aquatic biodegradation half-lives for metolachlor under aerobic and anaerobic conditions are 47 and 78 days, respectively(12). The disappearance of metolachlor in groundwater free of aquifer materials (e.g., sand) was very slow and the half-life was in the range of 548-1074 days(13).

*(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Wauchope RD et al; Rev Environ Contam Toxicol 123: 1-155 (1992) (3) Bowman BT; Environ Toxicol Chem 9: 453-61 (1990) (4) Ahrens W; Herbicide Handbook of the Weed Science Society of America. 7th ed Champaign, IL: Weed Science Society of America p. 199 (1994) (5) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9, 15-1 to 15-29 (1990) (6) Chesters G et al; Rev Environ Contam Toxicol 110: 1-74 (1989) (7) Kochany J, Maguire RJ; J Agric Food Chem 42: 406-412 (1994) (8) Hessler DP, Frimmel FH; pp. 121-3 in Amer Chem Soc. Div Environ Chem. Preprint 203rd ACS Nat Meet. Vol 32 (1992) (9) Gustafson DI; Environ Toxicol Chem 8: 339-57 (1989) (10) Franke C et al; Chemosphere 29: 1501-14 (1994) (11) Ellgehausen H et al; Ecotox Environ Safety 4: 134-57 (1980) (12) USEPA/OPPTS; Reregistration Eligibility Decisions (REDs) Database on Metolachlor (51218-45-2). USEPA 738-R-97-011. Available from, as of Jan 24, 2012: **https://www.epa.gov/pesticides/reregistration/status.htm** (13) Cavalier TC et al; Ground Water 29: 225-31 (1991)*

Hazardous Substances Data Bank (HSDB)

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), metolachlor, which has a vapor pressure of 3.14X10-5 mm Hg at 25 °C(2), will exist in both the vapor and particulate phases in the ambient atmosphere(SRC). Vapor-phase metolachlor is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals(SRC); the half-life for this reaction in air is estimated to be 7 hrs(SRC), calculated from its rate constant of 7.02X10-11 cu cm/molecule-sec at 25 °C(3). Particulate-phase metolachlor may be removed from the air by wet and dry deposition(SRC). Metolachlor absorbs light in the environmental spectrum and has the potential for direct photolysis in the atmosphere(SRC). Photolysis half-lives ranging from 8-22 days have been reported in the atmosphere(4).

(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) Wauchope RD et al; Rev Environ Contam Toxicol 123: 1-155 (1992) (3) Atkinson R; Environ Toxicol Chem 7: 435-62 (1988) (4) Kochany J, Maguire RJ; J Agric Food Chem 42: 406-412 (1994)

Hazardous Substances Data Bank (HSDB)

13.2.8 Environmental Biodegradation

AEROBIC: Under aerobic soil conditions, metolachlor degraded with a half-life of 67 days in a sandy loam soil(1). The rate of degradation of metolachlor in soil increases with an increase in soil moisture content, temperature and microbial activity(2,3). The degradation of metolachlor is slower in subsoils than in surface soil(2). Five metabolites of metolachlor including 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(hydroxyprop-2-yl)acetamide have been identified in soil(2). The aerobic aquatic biodegradation half-life of metolachlor was 47 days(1). The disappearance of metolachlor in groundwater free of aquifer materials (e.g., sand) was very slow(4,5). After a lag period of 10-12 months, metolachlor degraded with half-lives of 548-1074 days(5). In a study examining soils from agrochemical dealerships or railroad rights-of-way in central Iowa, rhizosphere soil samples, representing four plant families, were not able to mineralize large quantities (>8.5%) of 14C-metolachlor after 50 days(6). Samples were incubated in the dark at 20 °C with a metolachlor concentration of 50 ug/g(6). However, in a 14-day environmental chamber study with a 14 hr photoperiod, degradation of 10 ppm metolachlor, present as a mixture with trifluralin and atrazine, was shown to occur in non-vegetated soil (27% degradation) but not to the extent of the Kochia scoparia rhizosphere soil (48% degradation), suggesting that the rhizosphere of certain plant species may facilitate microbial degradation(7). Metolachlor was not biodegraded in contaminated soil from an agrochemical dealership in Iowa, 50 ug/g initial concentration (background concentration averaged 7 ug/g) had ending concentrations of 43 to 60 ug/g metolachlor after 160 days of incubation at 25 °C in the dark(8).

*(1) USEPA/OPPTS; Reregistration Eligibility Decisions (REDs) Database on Metolachlor (51218-45-2). USEPA 738-R-97-011. Available from, as of Jan 24, 2012: **https://www.epa.gov/pesticides/reregistration/status.htm** (2) Chesters G et al; Rev Environ Contam Toxicol 110: 1-74 (1989) (3) Zimdahl RL, Clark SK; Weed Sci 30: 545-8 (1982) (4) Konopka A, Turco R; Appl Environ Microbiol 57: 2260-8 (1991) (5) Cavalier TC et al; Ground Water 29: 225-31 (1991) (6) Anderson TA, Coats JR; J Environ Sci Health B30: 473-484 (1995) (7) Anderson TA et al; Chemosphere 28: 1551-7 (1994) (8) Anhalt JC et al; J Environ Sci Health: B35: 417-38 (2000)*

▸ Hazardous Substances Data Bank (HSDB)

ANAEROBIC: Metolachlor degraded with a half-life of 81 days in a sandy loam soil that was incubated under anaerobic conditions for 60 days at 25 °C following 30 days of aerobic incubation(1). The anaerobic aquatic biodegradation half-life for metolachlor was 78 days(1). The degradation rate constant for metolachlor was reported as -31.7/day with a half-life of 62 days in anaerobic wetland soil incubated for 112 days at 24 °C, the degradation rate constant in the aqueous phase was -0.017/day and half-life was 40 days(2).

*(1) USEPA/OPPTS; Reregistration Eligibility Decisions (REDs) Database on Metolachlor (51218-45-2). USEPA 738-R-97-011. Available from, as of Jan 24, 2012: **https://www.epa.gov/pesticides/reregistration/status.htm** (2) Seybold CA et al; J Environ Qual 30: 1271-7 (2001)*

▸ Hazardous Substances Data Bank (HSDB)

13.2.9 Environmental Abiotic Degradation

The rate constant for the vapor-phase reaction of metolachlor with photochemically-produced **hydroxyl** radicals has been estimated as 7.02X10-11 cu cm/molecule-sec at 25 °C(1). This corresponds to an atmospheric half-life of about 7 hours at an atmospheric concentration of 5X10+5 **hydroxyl** radicals per cu cm(1). The aqueous photolysis half-life was 70 days when exposed to natural sunlight and 0.17 day when exposed to artificial sunlight (450 watt **mercury** arc lamp with light intensity of 4500-4800 uW/sq cm)(2). The soil photolysis half-life of metolachlor when exposed to natural sunlight was 8 days; when exposed to artificial light conditions (**mercury** arc lamp with light intensity of 1600-2400 uW/sq cm) the half-life was 37 days(2).

*(1) Atkinson R; Environ Toxicol Chem 7: 435-62 (1988) (2) USEPA/OPPTS; Reregistration Eligibility Decisions (REDs) Database on Metolachlor (51218-45-2). USEPA 738-R-97-011. Available from, as of Jan 24, 2012: **https://www.epa.gov/pesticides/reregistration/status.htm***

▸ Hazardous Substances Data Bank (HSDB)

The photodegradation half-life of metolachlor was 8 days on sandy loam soil at 15-52 °C with natural light(1). Photodegradation is a major contributor to dissipation in the field, particularly under prolonged lack of rainfall when metolachlor remains on the soil surface(1). When metolachlor applied at 5.15 kg a.i./ha on glass slides coated with a silt loam soil was irradiated with natural sunlight and sunlamp, it photodecomposed with a half-life of 8 days and 7 days, respectively(2). However, the rise in temperature during irradiation caused 5% of the parent compound to volatilize(2). The photodegradation half-lives of metolachlor in organic-free, lake, and 5 mg/L dissolved organic matter **water** are 8, 11, and 22 days in summer natural light, respectively(3); and 54, 77, and 231 days in winter natural light, respectively(3). The 4 major photodegradation products in **water** are [**2-hydroxy-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide**]; [N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide]; [**4-(2-ethyl-6-methylphenyl)-5-methyl-3-morpholinone**]; [2-hydroxy-N-(2-ethyl-6-methylphenyl)acetamide](3). Humic substances in **water** retarded the photolysis of metolachlor in **water**(2-4). Photolysis half-lives of metolachlor in distilled **water**, seawater, river **water** and lake **water** irradiated outdoors were 193, 408, 578 and 693 hours, respectively; under simulated solar irradiation half-lives were 87, 161, 248 and 301 hours, respectively(5). The photodegradation half-life of metolachlor in distilled **water** was reduced to 48 hours with a **nitrate** ion concentration of 1.0 mg/L and to 8 hours with a **nitrate** ion concentration of 10.0 mg/L(5). The estimated hydrolysis half-life of metolachlor in **water** is 210 days(6). Hydrolysis of metolachlor was <5% in 100 days of testing at 20 °C at pH 4, 7 and 9(7). The hydrolysis rate of metolachlor at 20 °C in distilled water was <0.01 1/day coresponding to a half-life of >100 days(7).

(1) Ahrens W; Herbicide Handbook of the Weed Science Society of America. 7th ed Champaign, IL: Weed Science Society of America p. 199 (1994) (2) Chesters G et al; Rev Environ Contam Toxicol 110: 1-74 (1989) (3) Kochany J, Maguire RJ; J Agric Food Chem 42: 406-412 (1994) (4) Hessler DP, Frimmel FH; pp. 121-3 in Amer Chem Soc. Div Environ Chem. Preprint 203rd ACS Nat Meet. Vol 32 (1992) (5) Dimou AD et al; J agric Food Chem 53: 694-701 (2005) (6) Gustafson DI; Environ Toxicol Chem 8: 339-57 (1989) (7) Carlson DL et al; Food Chem 54: 4740-50 (2006)

▸ Hazardous Substances Data Bank (HSDB)

13.2.10 Environmental Bioconcentration

A whole body BCF for metolachlor in catfish (Ictalurus melas) was experimentally determined to be <1(1). The time required to attain equilibrium in catfish was found to be 3-4 days; and the depuration half-life in catfish was 1.2 days(1). In another study, a whole body metolachlor BCF of 69 was reported for fish, with a whole body elimination of 93% after 14 days depuration(2). A whole body BCF for metolachlor in bluegill (Lepomic macrochirus) exposed for 28 days was 74(3). Catfish BCFs of metolachlor were 6.5-9.0 for edible portions and 55-99 for viscera after a 30 day exposure(4). According to a classification scheme(5), these BCF values suggest bioconcentration in aquatic organisms is low to moderate(SRC).

*(1) Ellgehausen H et al; Ecotox Environ Safety 4: 134-57 (1980) (2) USEPA/OPPTS; Reregistration Eligibility Decisions (REDs) Database on Metolachlor (51218-45-2). USEPA 738-R-97-011. Available from, as of Jan 24, 2012: **https://www.epa.gov/pesticides/reregistration/status.htm** (3) Jackson SH et al; J Agric Food Chem 57: 958-67 (2009) (4) Chesters G et al; Rev Environ Contam Toxicol 110: 1-74 (1989) (5) Franke C et al; Chemosphere 29: 1501-14 (1994)*

▸ Hazardous Substances Data Bank (HSDB)

13.2.11 Soil Adsorption/Mobility

Koc values for metolachlor have been reported to range from 22 to 2320(1-3). In an 80 day field study using tropical soils of Brazil, Koc values were measured for metolachlor; Ustox soil (42.9-54.0% clay, 2.5-4.3% silt, 42.4-54.6% sand, 1.63-3.06% organic carbon) had an initial Koc of 186 and maximum Koc of 1530; Psamments soil (9.7-14.4% clay, 1.0-1.8% silt, 84.6-88.5% sand, 0.71-1.01% organic carbon) had an initial Koc of 122 and maximum Koc of 2320(1). Koc values for clay (4.8% organic matter, 42% clay and pH 5.9), sand (0.9% organic matter, 2.2% clay, and pH 6.5), sandy loam (5% organic matter, 9.2% clay, and pH 5.9), and loam (1.2% organic matter, 11.2% clay, and pH 7.6) soils are 68, 22, 74, and 110, respectively(2). Vegetative filter strip soil (37.9% sand, 31.9% silt, 30.2% clay, 4.2% organic carbon, pH 7.6) and cultivated soil (36.8% sand, 29.5% silt, 33.7% clay, 2.5% organic carbon, pH 7.6) from Texas had measured Koc values for metolachlor of 195.9 and 173.7, respectively(3). According to a classification scheme(4), these Koc values suggest that metolachlor is expected to have very high to slight mobility in soil(SRC). Metolachlor adsorbs more readily to muck or clay soils than to soils with low organic matter and clay content, and adsorbs more readily to organic matter than to clay(2). Experimental leaching and soil thin layer plate studies have shown that metolachlor absorbs weakly to moderately to soil and the leaching of metolachlor from soil is high to medium(5,6). In field experiments conducted with soybeans grown in Wisconsin, and corn in Iowa and California, no quantifiable metolachlor residues (limit of detection = 50 ppb) were found below 45 cm (18 in)(2). Leaching of metolachlor is generally not expected when soil organic matter is >2%(2). Leaching potentials were measured in six soil types on the Canary Island of Tenerife, potentials were 0.107 to 0.303 and is considered a leacher (> or = 0.2 to < or = 1)(7). Metolachlor had Kd values of 130.3, 32.9 and 30.9 mL/g with Bermuda grass, Weswood soil (course-silty, mixed, thermic, Fluventic Ustocherpt) and Houston black soil (fine, montmorilliontic, thermic, Udic Pellustert), respectively(8). Log Kom values ranged from 0.98 to 2.17 in 33 surface soils from Salamanca, Spain with a pH range of 4.4 to 7.7 and organic matter range of 0.43 to 2.59%(9).

(1) Laabs V, Amelung W; J Agric Food Chem 53: 7184-92 (2005) (2) Ahrens W; Herbicide Handbook of the Weed Science Society of America. 7th ed Champaign, IL: Weed Science Society of America p. 199 (1994) (3) Krutz JL et al; J Environ Qual 33: 939-45 (2004) (4) Swann RL et al; Res Rev 85: 17-28 (1983) (5) Chesters G et al; Rev Environ Contam Toxicol 110: 1-74 (1989) (6) Barnes CJ et al; J Environ Qual 21: 232-6 (1992) (7) Diaz-Diaz R et al; J Contam Hydrol 36: 1-30 (1999) (8) Dozier MC et al; Arch Environ Contam Toxicol 43: 292-5 (2002) (9) Crisanto T et al; Sci Total Environ 166: 69-76 (1995)

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Leaching of metolachlor in two Cuban soil types(1).

Soil Type	Soil Layer (cm)	Simulated annual rainfall (nm)	Leaching (%of total in column)
Red ferralitic	0-10	100	49.3
		200	29.3
		400	18.8
	10-20	100	28.4
		200	35.8
		400	43.1
	20-30	100	22.3
		200	34.8
		400	38.1
Brown plastic	0-10	100	52.5
		200	44.8
		400	47.0
	10-20	100	38.7
		200	46.2
		400	46.7
	20-30	100	8.8
		200	9.0
		400	6.3

(1) Kierksmeier G et al; in Pesticide Residues in Coastal Tropical Ecosystems. Taylor and Francis Group, New York, NY (2003)

▸ Hazardous Substances Data Bank (HSDB)

13.2.12 Volatilization from Water/Soil

The Henry's Law constant for metolachor is 9.0X10-9 atm-cu m/mole(1). This Henry's Law constant indicates that metolachlor is expected to be essentially nonvolatile from moist soil and water surfaces(2). However, volatilization of metolachlor from water in the laboratory and field was shown to occur when the temperature was 40 to 50 °C, reflecting the increase of Henry's Law constant with temperature(3). Metolachlor volatilization

was found to be affected by residue cover, spatial concentration on the surface, and timing of precipitation. Volatilization loss from two fields in the central Iowa Walnut Creek watershed was studied under contrasting tillage and pesticide application practices. One field was subjected to banded pesticide application and conventional tillage practices for corn that included leaving approx 30% corn residue on the surface over winter. The other field was subjected to broadcast application using ridge-till which allows most of the crop residue to remain over winter in the undisturbed ridges, approximately 80% soil coverage. Metolachlor was applied at 2.24 kg/ha to both fields. Based on the assumption that losses due to application drift and subsequent post-study volatilization losses were negligible, 6% and 22% applied metolachlor was volatilized in 315 hrs from the banded and broadcast fields, respectively(4). In a three year field study where metolachlor was applied to similar fields with varying soil moisture contents, it was observed that metolachlor volatilization increased with increasing soil moisture(5). Metolachlor is not expected to volatilize from dry soil surfaces(SRC) based upon a vapor pressure of 3.1X10-5 mm Hg(6).

(1) Chesters G et al; Environ Contam Toxicol 110: 1-74 (1989) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990) (3) El-Nahhal Y et al; Appl Clay Sci 14: 105-19 (1999) (4) Prueger JH et al; J Environ Qual 28: 75-81 (1999) (5) Gish TJ et al; J Environ Qual 38: 1785-95 (2009) (6) Wauchope RD et al; Rev Environ Contam Toxicol 123: 1-155 (1992)

Hazardous Substances Data Bank (HSDB)

13.2.13 Environmental Water Concentrations

SURFACE **WATER**: Metolachlor was detected in Lakes Erie and Ontario in 1991-2 at concentrations of 10-28 ng/L and 15 ng/L, respectively(1). Concentrations of metolachlor were reported in North American lakes as 4.3-22, 0.15-4.5, <0.002-1.4, and <0.002-1.13 ng/L in 3 of 3 lakes with agricultural input (42-44 deg N latitude), 12 of 14 remote mid-latitude lakes (40-50 deg N latitude), 6 of 7 sub-arctic lakes (50-60 deg N latitude), and 5 of 6 arctic lakes (>70 deg N latitude), respectively, samples were obtained July 1998 to Sept 2001(2). Metolachlor was detected in 42 out of 214 samples collected in 8 urban streams sampled in the US at a maximum concentration of 0.49 ug/L(3). Surface **water** samples taken from US streams in the Great Lakes basin tested positive for metolachlor in 50.4% of 393 samples taken 1994 to 2000 at concentrations of 0.0007 to 1.6000 ug/L(4). Metolachlor was detected at an avg concentration of 0.23 ppb and a concentration range trace-2.70 ppb in 12 of 31 river waters in NJ(5). Metolachlor was detected in all 39 samples taken from Cow Castle Creek, SC from Feb 1996 to Oct 1996 and again Feb 4, 1998 at a concentration range of 0.004 to 1.1 ug/L, concentrations ranged from <0.05 to 0.93 ug/L in 8 of 12 samples taken April 1997 to March 1998(6). Metolachlor was detected in 58% of the samples collected from 12 supply streams in North Carolina at a maximum concentration of 2.23 ug/L(7). Five separate collection cruises on the Choptank River, MD were conducted on May 10, June 15, July 24, Aug 29 and Dec 6, 2000, metolachlor concentrations were reported as <3.6 to 850 ng/L(8). Metolachlor was detected in 5.8% of samples taken from the Kisco river with a maximum concentration of 0.011 ug/L and in 32% of samples taken from the middle branch of the Croton River with a maximum concentration of 0.0066 ug/L, samples were collected May 2000 to Feb 2001, rivers are part of New York City water supply system(9).

(1) Schottler SP, Eisenreich SJ; Environ Sci Technol 28: 2228-32 (1994) (2) Muir DCG et al; Environ Toxicol Chem 23: 2421-32 (2004) (3) Hoffman RS et al; Environ Toxicol Chem 19: 2249-58 (2000) (4) Klecka G et al; Rev Environ Contam Toxicol 207: 1-93 (2010) (5) Mattern GC et al; J Assoc Off Anal Chem 74: 982-86 (1991) (6) Puckett LJ, Hughes WB; J Environ Qual 34: 2278-92 (2005) (7) Holman, RE et al; J Am Water Resour 36: 75-85 (2000) (8) Kuang Z et al; J Environ Qual 32: 1611-22 (2003) (9) Phillips PJ, Bode RW; Pest Manag Sci 60: 531-43 (2004)

Hazardous Substances Data Bank (HSDB)

SURFACE **WATER**: It was detected at a concentration range 0.046-0.273 ppb in **water** from the Mississippi River and its tributaries in 1988(1). During 1984-1985, the max. concentration of metolachlor in waters from three stations along the Cedar River, Iowa due to overland flow was <10 ppb(2). Metolachlor was detected at mean concentration 1.23 ppb and 0.93 ppb in water from Upper Tuttle Creek Lake and Lower Tuttle Creek Lake, respectively in Kansas(3). The concentration range of metolachlor in Honey Creek, Sandusky River and Maumee River during 1983-1986 was not detected to 95.7 ppb(4). Metolachlor was detected at <0.05 to 0.42 ug/L in agricultureal streams of Midwest US in samples taken Aug 1997(5). Metolachlor degradation products, metolachlor ethanesulfonic acid and metolachlor oxanilic acid were detected in the same samples at <0.2 to 6.7 ug/L and <0.2 to 1.3 ug/L, respectively(5). Metolachlor was not detected (detection limit 0.5 ug/L) in 18 streams in north-central and northwestern Arkansas, samples were collected March, April and August of 2004(6). Metolachlor was detected in the mean concentration range 0.87-1.8 ppb in the Sacramento River above confluence with the San Joaquin River(7). Metolachlor was detected in 71% of 142 samples from four locations in the San Joaquin River basin at a maximum concentration of 1.6 ug/L (detection limit 0.002 ug/L), samples were taken from Jan to Dec 1993(8). Metolachlor was detected in 13 of 98 surface water samples taken from the Yakima River basin, WA at concentrations of <0.002 to 0.009 ug/L in samples taken May 1999 to Jan 2000(9).

(1) Pereira WE, Rostad CE; Environ Sci Technol 24: 1400-6 (1990) (2) Squillace PJ, Thurman EM; Environ Sci Technol 26: 538-45 (1992) (3) Arruda JA et al; Bull Environ Contam Toxicol 41: 617-24 (1988) (4) Great Lakes Water Quality Board; 1987 Report on Great Lakes Water Quality Appendix B, Great Lakes Surveillance Vol I. Report of the International Joint Commission p. 2: 4-3 (1989) (5) Kalkhoff SJ et al; J Environ Qual 32:1025-35 (2003) (6) Haggard BE et al; J Environ Qual 35:1078-87 (2006) (7) Chesters G et al; Rev Environ Contam Toxicol 110: 1-74 (1989) (8) Dubrovsky NM et al; in Agrochemical Fate and Movement, Steinheimer T et al, eds., Amer Chem Soc, Washington, DC pp 306-22 (2000) (9) Ebbert JC, Embrey SS; in Water-Resource Investigative Report 01-4211, US Dept Int, US Geol Survey, Portland, OR pp 1-49 (2001)

Hazardous Substances Data Bank (HSDB)

GROUNDWATER: As of 1984, statewide screening of community and private wells in Wisconsin detected metolachlor in one well **water**(1). Metolachlor was detected in well waters in Nebraska with a frequency of <1% and at a concentration range of not detected to 2.3 ug/L and a median concentration of 0.06 ug/L(2). Metolachlor has also been detected in the concentration range of 0.10 to 4.5 ug/L in groundwater from Big Springs watershed in Iowa(2,3). In some cases, artificial recharging of groundwater by farmland runoff may have caused metolachlor contamination in Nebraska groundwater(4). In Kansas, 2% of public water supply wells contained metolachlor at a max concentration of 1.6 ug/L(5). In a pilot study during 1987-1988, metolachlor was detected in one well water from Comanche county, TX at an avg concentration of 5.5 ug/L(6). Metolachlor was detected in groundwater samples from 90% of 28 agrochemical dealership sites in Iowa at a max concentration of 25,000 ug/L(7). Metolachlor was detected in 15 of 53 groundwater samples taken Nov 1997 and April 1998 from the Cow Castle Creek, SC riparian and upland zones, concentrations ranged from <0.002 to 0.25 ug/L(8). A study of 86 wells across Iowa reported metolachlor in 9.3% of the samples with a maximum concentration of 3.2 ug/L(15). Metolachlor was reported in ground water samples from Cedar River alluvial aquifer, Cedar Rapids, IA at <0.05 to 0.33 ug/L, samples were taken June to Aug 1998(10). Median levels of metolachlor were estimated as 0.01 ug/L in the Great Valley Potomac River Basin and reported as <0.01 ug/L in the shallow and deep coastal plains of the Delmarva Penisula, Mid-Atlantic, samples taken 1988 to 2005(11). Metolachlor was

not detected in 20 orchard and 34 public supply groundwater wells sampled 1993 to 1995 and 2002 to 2003 from the Central Columbia Plateau, WA(12). Metolachlor was detected in three of 18 row crop groundwater wells sampled 1993 to 1995 and in one of the same 18 wells were tested again 2002 to 2003, detection limits varied and were not reported as this was a trend study(12).

(1) Krill RM, Sonzogni WC; J Am Water Works Assoc 78: 70-5 (1986) (2) Ritter WF; J Environ Sci Health 25: 1 (1990) (3) Chesters G et al; Rev Environ Contam Toxicol 110: 1-73 (1989) (4) Exner ME; GWMR 10: 147-59 (1990) (5) Hallberg GR; Agric Ecosyst Environ 26: 299-367 (1989) (6) Aurelius LA; Testing for pesticide residues in Texas well water. Texas Dept of Agriculture, Austin, TX p. 13 (1989) (7) Anderson TA et al; 87th Annual Meeting and Exhibition in Cincinnati, OH. June 19-24. Air and Waste Management Assoc, 94-TP45B.08 (1994) (8) Puckett LJ, Hughes WB; J Environ Qual 34: 2278-92 (2005) (9) Kolpin DW et al; Ground Water 42: 601-8 (2004) (10) Boyd RA; Water Resour Bull 99-4018B: 289-300 (1999) (11) Debrewer LM et al; J Environ Qual 37: S296-308 (2008) (12) Frans L; J Environ Qual 37: S273-80 (2008)

▸ Hazardous Substances Data Bank (HSDB)

GROUNDWATER: Several rural and farm wells in Ontario, Canada were contaminated with metolachlor at concentrations ranging from not detected to 110 ppb(1,2). Metolachlor was detected in five samples taken from 100 wells over a one year sampling study done May 1996 to April 1997 in the Imathia area of Greece at a maximum concentration of 0.041 ug/L(3). Surficial aquifer samples from six different farms in Northern Italy had metolachlor levels of <0.02 to 0.14 ug/L, samples were aquired in the spring and summer of 1999 and 2000(4). Metolachlor was detected in surficial groundwater samples taken March 1999 at concentrations of <0.02 to 0.09 ug/L from 11 locations in Bergamo Province, Italy and at concentrations of <0.02 to 1.02 ug/L from 25 locations in Lodi Province, Italy(5). Metolachlor was detected in 17 of 80 monitoring well samples from five northern areas of Greece (Pieria, Thessaloniki, Serres, Kavala, Evros) at conentrations of <0.005 to 0.547 ug/L(6).

(1) Chesters G et al; Rev Environ Contam Toxicol 110: 1-73 (1989) (2) Frank R et al; Bull Environ Contam Toxicol 44: 410-9 (1990) (3) Albanis TA et al; J Chromatogr 823: 59-71 (1998) (4) BarraCaracciolo A et al; Environ Pollut 134: 525-34 (2005) (5) Guzzella L et al; Environ Pollut 142: 344-53 (2006) (6) Papastergiou A, Papadopoulou-Mourkidou E; Environ Sci Technol 35: 63-9 (2001)

▸ Hazardous Substances Data Bank (HSDB)

For more Environmental **Water** Concentrations (Complete) data for METOLACHLOR (8 total), please visit the **HSDB record page**.

▸ Hazardous Substances Data Bank (HSDB)

13.2.14 Effluent Concentrations

Metolachlor was detected in soil used for potato crop production at concentrations of 11-107 ug/kg (43%) and >107 ug/kg (53%) at 1 day after application; 11-107 ug/kg (36%) and >107 ug/kg (27%) at 42 days after application; 11-107 ug/kg (30%) and >107 ug/kg (20%) at 1 day after application(1). Metolachlor was detected at 90% of 28 agrochemical dealership sites in Iowa at a max concentration of 856 ug/g(2). Metolachlor was detected at 9.6 ug/g in soil at a agrochemical dealership in Iowa(3). Metolachlor was detected in 90% of the groundwater samples taken from 28 agrochemical dealership sites in Iowa at a maximum concentration of 25,000 ug/L(4).

(1) Burgrad DJ et al; Weed Sci 41: 648-655 (1993) (2) Anderson TA et al; 87th Annual Meeting and Exhibition in Cincinnati, OH. June 19-24. Air and Waste Management Assoc, 94-TP45B.08 (1994) (3) Anderson TA et al; Chemosphere 28:1551-7 (1994) (4) Anderson TA et al; IN: Air Waste Manage Assoc 87th Annual Meeting, Cincinnati, OH, June 19-24, 1994. 94-TP45B.08 (1994)

▸ Hazardous Substances Data Bank (HSDB)

13.2.15 Sediment/Soil Concentrations

SEDIMENT: Sediment samples from Beijing Guanting Reservoir taken at seven locations in Sept and Nov 2003, and June and Aug 2004 contained metolachlor at 65.8 to 297 pg/g(1).

(1) Xue N et al; Chemosphere 61: 1594-1606 (2005)

▸ Hazardous Substances Data Bank (HSDB)

SOIL: Metolachlor was detected in soil used for potato crop production at concentrations of 11-107 ug/kg (43%) and >107 ug/kg (53%) at 1 day after application; 11-107 ug/kg (36%) and >107 ug/kg (27%) at 42 days after application; 11-107 ug/kg (30%) and >107 ug/kg (20%) at 1 day after application(1). Metolachlor was detected at 90% of 28 agrochemical dealership sites in Iowa at a max concentration of 856 ug/g(2).

(1) Burgrad DJ et al; Weed Sci 41: 648-655 (1993) (2) Anderson TA et al; 87th Annual Meeting and Exhibition in Cincinnati, OH. June 19-24. Air and Waste Management Assoc, 94-TP45B.08 (1994)

▸ Hazardous Substances Data Bank (HSDB)

13.2.16 Atmospheric Concentrations

URBAN/SUBURBAN: In 1984, the concentration of metolachlor in interstitial air of fogwater in Beltsville, MD was <0.4X10-3 ng/cu m(1). Metolachlor was detected in urban air samples (levels not reported) collected in Mississippi, April to Sept 1995(2). Metolachlor was identified, not quantified, in approximately 10% of the atmospheric samples obtained in Jackson, MS, 100% of the atmospheric samples obtained in Iowa City, IA as well as 40% of the samples from Minneapolis, MN(3). Air samples collected once a week from April 18 to Dec 19, 2000, near the Choptank River in Cambridge, MD had reported metolachlor concentrations of 63 to 10,200 pg/cu m

in 100% of the samples(4). From 2000 to 2002, atmospheric samples were taken in urban, suburban and rural locations of eastern Iowa, metolachlor was reported in 40% of the samples with a concentration range of <0.0059 to 27.5 ng/cu m(5).

PMID:3808063

(1) Glotfelty DE et al; Nature 325: 602-5 (1987) (2) Coupe RH et al; Water Resour Bull 99-4018B: 301-12 (1999) (3) Foreman WT et al; Sci Total Environ 248: 213-226 (2000) (4) Kuang Z et al; J Environ Qual 32:1611-22 (2003) (5) Peck AM, Hornbuckle KC; Environ Sci Technol 39: 2952-9 (2005)

Hazardous Substances Data Bank (HSDB)

RURAL/REMOTE: The concentration of metolachlor in air sampled from Ottawa to southern Ontario (Canada) ranged from not detected to 9.8 ng/cu m in June 1993 and July 1994(1). Weekly atmospheric samples (May 4 to June 29, 2004) taken in St Damase, Yamaska basin area of Quebec, Canada had metolachlor concentrations of 3031.1 to 19,061.7 pg/cu m, monthly samples taken June 29 to Sept 21 were reported as 266 to 3364 pg/cu m(2). From 2000 to 2002, atmospheric samples were taken in urban, suburban and rural locations of eastern Iowa, metolachlor was reported in 40% of the samples with a concentration range of <0.0059 to 27.5 ng/cu m(3). Metolachlor was not detected in high-volume air samples taken from four locations in Saskatchewan, Canada(4). Air samples taken across Canadian agricultural area reported metolachlor concentrations as not detected (detection limit 10.0 pg/cu m) to 76.4, 242 to 4860, not detected to 1130, 249 to 3640, and 222 to 2610 pg/cu m in air samples taken in Abbotsford, Egbert, Vineland, St. Anicet and Baie St. Francis, respectively, in 2004(5). Metolachlor was not detected in Bratt's Lake or Kensington in 2004. In 2005, metolachlor concentrations were reported as 415 to 9940, not detected to 2440, 69.7 to 365, 4030 to 23,6000, and 6290 to 12,300 pg/cu m in air samples taken in Egbert, Vineland, Downsview, St. Anicet and Baie St. Francis, respectively(5). Metolachlor was not detected in Abbotsford, Bratt's Lake, or Kensington in 2005(5).

(1) Zhu T et al; Environ Sci Technol 32: 1032-1038 (1998) (2) Aulagnier F et al; Sci Total Environ 394: 338-48 (2008) (3) Peck AM, Hornbuckle KC; Environ Sci Technol 39: 2952-9 (2005) (4) Waite DT et al; Chemosphere 58: 693-701 (2005) (5) Yao Y et al; Environ Sci Technol 42(16): 5931-7 (2008)

Hazardous Substances Data Bank (HSDB)

SOURCE DOMINATED: Metolachlor was detected in agricultural air samples (levels not reported) collected in Mississippi, April to Sept 1995(1). Metolachlor was identified, not quantified, in approximately 80% of the atmospheric samples obtained from Rolling Fork, MS, 90% of the atmospheric samples obtained from Cedar Rapids, IA, as well as about 60% of the samples from Princeton, MN(2).

(1) Coupe RH et al; Water Resour Bull 99-4018B: 301-12 (1999) (2) Foreman WT et al; Sci Total Environ 248: 213-226 (2000)

Hazardous Substances Data Bank (HSDB)

13.2.17 Food Survey Values

The Food and Drug Administration's regulatory monitoring program for the period 1982-1986 detected metolachlor in raw agricultural commodities collected in the United States(1). However, neither the commodities that contained metolachlor nor the levels in these commodities were reported(1). Metolachlor was not found (detection limit 0.01 mg/kg) in samples of composite vegetables representing nine vegetable commodities collected from Ontario, Canada between 1980-1985(2). In 2007, 8172 samples of fresh produce and 1562 samples of processed produce were analyzed: 528 banana, 504 blueberry, 20 frozen blueberry, 419 cherry, 739 green bean, 359 kale green, 563 nectarine, 555 peach, 800 frozen potato and 741 tomato samples did not contain metolachlor, however two of 731 broccoli, 12 of 739 celery and one of 335 collard greens tested positive for metolachlor(3).

(1) Yess NJ et al; J Assoc Off Anal Chem 74: 273-80 (1991) (2) Frank R et al; J Assoc Off Anal Chem 70: 1081-6 (1987) (3) USDA Pesticide Data Program, Annual Summary, Calander Year 2007; Available from, as of Jan 24, 2012: https://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5074338

Hazardous Substances Data Bank (HSDB)

13.2.18 Fish/Seafood Concentrations

Although present in water, metolachlor was not detected in fish from Tuttle Creek Lake, a major tributary of the Kansas River, KS(1). Metolachlor was not detected (detection limit not reported) in common carp, largemouth bass, smallmouth buffalo, spotted sucker and yellow bullhead catfish taken from lakes and one creek in the Sparta National Guard Armory, IL(2).

PMID:3224183

(1) Arruda JA et al; Bull Environ Contam Toxicol 41: 617-24 (1988) (2) Ownby DR et al; Bull Environ Contam Toxicol 73: 802-9 (2004)

Hazardous Substances Data Bank (HSDB)

13.2.19 Other Environmental Concentrations

Metolachlor was detected in dry deposition samples collected at a farm location outside of Iowa City, at concentrations of 0.2-0.25 ug(1). Metolachlor was not detected in dry deposition samples collected in Iowa City, at a remote park (Macbride) outside of Iowa City, and at Oakdale (University of Iowa) samples were taken May 1997(1). Surface and settled dust wipe samples taken from homes in Cortland and Tompkins Counties, NY, in 1999

did not contain metolachlor(2). Carpet dust samples tested positive in 10 of 10 samples taken on both first and second visits with metolachlor levels of 0.1 to 10.0 ug/sq m and 0.1 to 8.7 ug/sq m, respectively(2). Metolachlor was detected in 21.4% of 112 house dust samples from Iowa residences at a concentration range of 27.8 to 3180 ng/g(3).

(1) Hochstedler ME et al; in Agrochemical Fate and Movement, Steinheimer T et al, eds., Amer Chem Soc, Washington, DC pp 217-31 (2000) (2) Lemley AT et al; Bull Environ Contam Toxicol 69:155-63 (2002) (3) Ward MH et al; Environ Health Perspect 114(6): 893-7 (2006)

▶ Hazardous Substances Data Bank (HSDB)

13.2.20 Probable Routes of Human Exposure

Occupational exposure to metolachlor may occur through inhalation and dermal contact with this compound at workplaces where metolachlor is produced or used. Monitoring data indicate that the general population may be exposed to metolachlor via inhalation of ambient air, ingestion of food and drinking **water**, and dermal contact with this herbicides containing metolachlor. (SRC)

▶ Hazardous Substances Data Bank (HSDB)

13.2.21 Body Burden

Metolachlor was detected in maternal serum samples at 0.007 to 1.96 ng/g and in corresponding cord serum at 0.007 to 2.37 ng/g(1).

(1) Barr DB et al; Sci Total Environ 408(4): 790-5 (2010)

▶ Hazardous Substances Data Bank (HSDB)

14 Associated Disorders and Diseases

- Comparative Toxicogenomics Database (CTD)

Associated Occupational Diseases with Exposure to the Compound

Contact dermatitis, allergic [Category: Skin Disease]

- Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

15 Literature

15.1 NLM Curated PubMed Citations

PubChem

15.2 Springer Nature References

Springer Nature

15.3 Thieme References

- Thieme Chemistry

15.4 Wiley References

- Wiley

15.5 Depositor Provided PubMed Citations

PubChem

15.6 Metabolite References

Human Metabolome Database (HMDB)

15.7 Chemical Co-Occurrences in Literature

PubChem

15.8 Chemical-Gene Co-Occurrences in Literature

PubChem

15.9 Chemical-Disease Co-Occurrences in Literature

PubChem

16 Patents

16.1 Depositor-Supplied Patent Identifiers

PubChem

Link to all deposited patent identifiers

PubChem

16.2 WIPO PATENTSCOPE

Patents are available for this chemical structure:

https://patentscope.wipo.int/search/en/result.jsf?inchikey=WVQBLGZPHOPPFO-UHFFFAOYSA-N

PATENTSCOPE (WIPO)

17 Interactions and Pathways

17.1 Chemical-Target Interactions

- Comparative Toxicogenomics Database (CTD); Drug Gene Interaction database (DGIdb); Toxin and Toxin Target Database (T3DB)

18 Biological Test Results

18.1 BioAssay Results

PubChem

19 Taxonomy

- Natural Product Activity and Species Source (NPASS)

20 Classification

20.1 MeSH Tree

Medical Subject Headings (MeSH)

20.2 ChEBI Ontology

ChEBI

20.3 KEGG: Pesticides

KEGG

20.4 ChemIDplus

ChemIDplus

20.5 CAMEO Chemicals

CAMEO Chemicals

20.6 ChEMBL Target Tree

ChEMBL

20.7 UN GHS Classification

- UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

20.8 EPA CPDat Classification

- EPA Chemical and Products Database (CPDat)

20.9 NORMAN Suspect List Exchange Classification

- NORMAN Suspect List Exchange

20.10 CCSBase Classification

- CCSbase

20.11 EPA DSSTox Classification

- EPA DSSTox

20.12 EPA Substance Registry Services Tree

- EPA Substance Registry Services

21 Information Sources

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CAMEO Chemical Reactivity Classification
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Metolachlor [ANSI:BSI:ISO]
https://pubchem.ncbi.nlm.nih.gov/substance/?source=chemidplus&sourceid=0051218452

(aS,5S)-Metolachlor
https://pubchem.ncbi.nlm.nih.gov/substance/?source=chemidplus&sourceid=0082535908

ChemIDplus Chemical Information Classification
https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

4. EPA DSSTox

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https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

Metolachlor
https://comptox.epa.gov/dashboard/DTXSID4022448

CompTox Chemicals Dashboard Chemical Lists
https://comptox.epa.gov/dashboard/chemical-lists/

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2-chloro-2'-ethyl-N-(2-methoxy-1-methylethyl)-6'-methylacetanilide
https://echa.europa.eu/substance-information/-/substanceinfo/100.051.856

6. FDA Global Substance Registration System (GSRS)

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METOLACHLOR
https://gsrs.ncats.nih.gov/ginas/app/beta/substances/X0I01K05X2

7. ## Hazardous Substances Data Bank (HSDB)

METOLACHLOR
https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6706

8. ## ILO International Chemical Safety Cards (ICSC)

METOLACHLOR
https://www.ilo.org/dyn/icsc/showcard.display?p_version=2&p_card_id=1360

9. ## Haz-Map, Information on Hazardous Chemicals and Occupational Diseases

Metolachlor
https://haz-map.com/Agents/1091

10. ## ChEBI

2-chloro-N-(2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl)acetamide
http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:83645

ChEBI Ontology
http://www.ebi.ac.uk/chebi/userManualForward.do#ChEBI%20Ontology

11. ## Toxin and Toxin Target Database (T3DB)

Metolachlor
http://www.t3db.ca/toxins/T3D1089

12. ## CCSbase

Metolachlor

CCSbase Classification
https://ccsbase.net/

13. ## NORMAN Suspect List Exchange

metolachlor

NORMAN Suspect List Exchange Classification
https://www.norman-network.com/nds/SLE/

14. ## ClinicalTrials.gov

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https://clinicaltrials.gov/

15. ## Comparative Toxicogenomics Database (CTD)

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https://ctdbase.org/detail.go?type=chem&acc=C051786

16. ## Drug Gene Interaction database (DGIdb)

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The data used in DGIdb is all open access and where possible made available as raw data dumps in the downloads section.
http://www.dgidb.org/downloads

METOLACHOR
https://www.dgidb.org/drugs/METOLACHOR

17. ## EPA Chemical and Products Database (CPDat)

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https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

Metolachlor
https://comptox.epa.gov/dashboard/DTXSID4022448#exposure

EPA CPDat Classification
https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

18. ## EPA Pesticide Ecotoxicity Database

LICENSE

https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

https://ecotox.ipmcenters.org/

19. ## EU Pesticides Database

Metolachlor
https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event=as.details&as_id=876

20. ## EPA Regional Screening Levels for Chemical Contaminants at Superfund Sites

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https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

Metolachlor
https://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search

Metolachlor
https://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search?tool=rml

21. ## NJDOH RTK Hazardous Substance List

metolachlor
http://nj.gov/health/eoh/rtkweb/documents/fs/3374.pdf

22. ## USGS Columbia Environmental Research Center

LICENSE

https://www.usgs.gov/foia

METOLACHLOR
https://www.cerc.usgs.gov/data/acute/qrychemdesc.asp?Chemical=M0160

23. ## Human Metabolome Database (HMDB)

> LICENSE
>
> HMDB is offered to the public as a freely available resource. Use and re-distribution of the data, in whole or in part, for commercial purposes requires explicit permission of the authors and explicit acknowledgment of the source material (HMDB) and the original publication (see the HMDB citing page). We ask that users who download significant portions of the database cite the HMDB paper in any resulting publications.
>
> http://www.hmdb.ca/citing

Metolachlor
http://www.hmdb.ca/metabolites/HMDB0254678

HMDB0254678_msms_2227849
https://hmdb.ca/metabolites/HMDB0254678#spectra

24. ## NIST Mass Spectrometry Data Center

> LICENSE
>
> https://www.nist.gov/srd/public-law

Metolachlor
http://www.nist.gov/srd/nist1a.cfm

25. ## Japan Chemical Substance Dictionary (Nikkaji)

http://jglobal.jst.go.jp/en/redirect?Nikkaji_No=J1.898H

26. ## MassBank Europe

> LICENSE
>
> https://github.com/MassBank/MassBank-web/blob/main/MassBank-Project/LICENSE.txt

WVQBLGZPHOPPFO-UHFFFAOYSA-N
https://massbank.eu/MassBank/Result.jsp?inchikey=WVQBLGZPHOPPFO-UHFFFAOYSA-N

27. ## MassBank of North America (MoNA)

> LICENSE
>
> The content of the MoNA database is licensed under CC BY 4.0.
>
> https://mona.fiehnlab.ucdavis.edu/documentation/license

Metolachlor
https://mona.fiehnlab.ucdavis.edu/spectra/browse?query=exists(compound.metaData.name:%27InChIKey%27%20and%20compound.metaData.value:%27WVQBLGZPHOPPFO-UHFFFAOYSA-N%27)

28. ## Metabolomics Workbench

Metolachlor
https://www.metabolomicsworkbench.org/data/StructureData.php?RegNo=67472

29. ## Natural Product Activity and Species Source (NPASS)

Metolachor
https://bidd.group/NPASS/compound.php?compoundID=NPC316582

30. ## NIOSH Manual of Analytical Methods

> LICENSE
>
> The information provided using CDC Web site is only intended to be general summary information to the public. It is not intended to take the place of either the written law or regulations.
>
> https://www.cdc.gov/Other/disclaimer.html

51218-45-2
https://www.cdc.gov/niosh/docs/2003-154/pdfs/5602.pdf

51218-45-2
https://www.cdc.gov/niosh/docs/2003-154/pdfs/9200.pdf

51218-45-2
https://www.cdc.gov/niosh/docs/2003-154/pdfs/9201.pdf

31. ## SpectraBase

2-CHLORO-N-(2-ETHYL-6-METHYL-PHENYL)-N-(2-METHOXY-1-METHYLETHYL)ACETAMIDE
https://spectrabase.com/spectrum/J1QNMX1M0pG

Metolachlor
https://spectrabase.com/spectrum/HmEMY7jIC5w

aS,N-(1S)(+)-2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)-o-ACETOTOLUIDIDE
https://spectrabase.com/spectrum/5jaSZgh2BOF

aR,N-(1S)(-)-2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)-o-ACETOTOLUIDIDE
https://spectrabase.com/spectrum/FN0PyMY6aiZ

aRS, N-(1S)(-)-2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)-o-acetotoluidide
https://spectrabase.com/spectrum/BmHQGRsBTqb

aRS, N-(1R)(+)-2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)-o-acetotoluidide
https://spectrabase.com/spectrum/BKBm5nYeyrU

aRS, N-(1S)(-)-2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)-o-ACETOTOLUIDIDE
https://spectrabase.com/spectrum/EOTlZbkG5aR

aRS, N-(1R)(+)-2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)-o-ACETOTOLUIDIDE
https://spectrabase.com/spectrum/2p3UtuvQ8Kl

O-ACETOTOLUIDIDE, 2-CHLORO-6'-ETHYL- N-/2-METHOXY-1-METHYLETHYL/-, ARS,- N-/1S//MINUS/-,
https://spectrabase.com/spectrum/L7IJruDYxs4

32. ## NITE-CMC

2-chloro-2'-ethyl-N-(2-methoxy-1-methylethyl)-6'-methylacetanilide - FY2006
https://www.nite.go.jp/chem/english/ghs/06-imcg-0369e.html

2-chloro-2'-ethyl-N-(2-methoxy-1-methylethyl)-6'-methylacetanilide; Metolachlor - FY2020
https://www.nite.go.jp/chem/english/ghs/20-mhlw-2100e.html

33. ## Springer Nature

https://pubchem.ncbi.nlm.nih.gov/substance/?source=15745&sourceid=19049000-133220355
https://pubchem.ncbi.nlm.nih.gov/substance/?source=15745&sourceid=19049000-133235075

34. ## The National Institute for Occupational Safety and Health (NIOSH)

o-Acetotoluidide, 2-chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)-
https://www.cdc.gov/niosh-rtecs/AN345670.html

35. ## Thieme Chemistry

https://pubchem.ncbi.nlm.nih.gov/substance/?source=22163&sourceid=19049000-133222685

36. ## USDA Pesticide Data Program

Metolachlor
https://www.ams.usda.gov/datasets/pdp/pdpdata

37. ## Wikidata

Metolachlor
https://www.wikidata.org/wiki/Q409598

38. ## Wikipedia

Metolachlor
https://en.wikipedia.org/wiki/Metolachlor

39. ## Wiley

https://pubchem.ncbi.nlm.nih.gov/substance/?source=wiley&sourceid=123887

40. PubChem
https://pubchem.ncbi.nlm.nih.gov

41. Medical Subject Headings (MeSH)

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https://www.nlm.nih.gov/copyright.html

metolachlor
https://www.ncbi.nlm.nih.gov/mesh/67051786

MeSH Tree
http://www.nlm.nih.gov/mesh/meshhome.html

Herbicides
https://www.ncbi.nlm.nih.gov/mesh/68006540

42. KEGG

LICENSE

Academic users may freely use the KEGG website. Non-academic use of KEGG generally requires a commercial license

https://www.kegg.jp/kegg/legal.html

Pesticides
http://www.genome.jp/kegg-bin/get_htext?br08007.keg

43. UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

GHS Classification Tree
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

44. ChEMBL

LICENSE

Access to the web interface of ChEMBL is made under the EBI's Terms of Use (http://www.ebi.ac.uk/Information/termsofuse.html). The ChEMBL data is made available on a Creative Commons Attribution-Share Alike 3.0 Unported License (http://creativecommons.org/licenses/by-sa/3.0/).

http://www.ebi.ac.uk/Information/termsofuse.html

ChEMBL Protein Target Tree
https://www.ebi.ac.uk/chembl/g/#browse/targets

45. EPA Substance Registry Services

LICENSE

https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

EPA SRS List Classification
https://sor.epa.gov/sor_internet/registry/substreg/LandingPage.do

46. PATENTSCOPE (WIPO)

SID 403413230
https://pubchem.ncbi.nlm.nih.gov/substance/403413230

47. NCBI
https://www.ncbi.nlm.nih.gov/projects/linkout

Attachment B

IRIS File

Metolachlor; CASRN 51218-45-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Metolachlor

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	10/01/1990
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name —Metolachlor
CASRN — 51218-45-2
Last Revised — 10/01/1990

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: The Oral RfD for metolachlor may change in the near future pending the outcome of a further review now being conducted by the RfD/RfC Work Group.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weight gain **2-Year Rat Feeding Study** **Ciba-Geigy, 1983**	NOEL: 300 ppm (15 mg/kg/day) LEL: 3000 ppm (150 mg/kg/day)	100	1	1.5E-1 mg/kg/day
Reduced pup weights and parental food consumption **2-Generation Rat Reproduction Study** **Ciba-Geigy, 1981**	NOEL: 300 ppm (15 mg/kg/day) LEL: 1000 ppm (50 mg/kg/day)			

* Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

I.A.2. Principal and Supporting Studies (Oral RfD)

Ciba-Geigy Corporation. 1983. MRID No. 00129377. Ciba-Geigy Corporation. 1981. MRID No. 00080897. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Albino CD rats were divided into four groups and fed diets containing 0 (70 animals/sex), 30 (60 animals/sex), 300 (60 animals/sex), and 3000 (70 animals/sex) ppm (0, 1.5, 15, and 150 mg/kg/day) of technical metolachlor for 2 years (Ciba-Geigy, 1983). The apparent increase in the incidence of "testicular atrophy" in male rats that died on test in this study is of doubtful toxicological significance. This finding was not present at final sacrifice, and historical control data demonstrate that this finding is relatively common in rats. Therefore, the NOEL for this study is 300 ppm, based on decreased body weight gain in rats fed 3000 ppm, the highest dose tested.

Metolachlor technical was fed in the diet at dose levels of 0, 30, 300, or 1000 ppm (0, 1.5, 15, and 50 mg/kg/day) to Charles River CD strain albino rats (15 males and 30 females/group) beginning at 32 days (Ciba-Geigy, 1981). Animals were mated after either 14 weeks (F0) or 17 weeks (F1) on test. Mating occurred once per generation. The F1 parental animals were randomly selected from the F1a litter after weaning of F1a. F0 males were sacrificed after 135 days on test and F0 females were sacrificed after 164 days on test. Gross examination was conducted on all F0 males and females that displayed "untoward developmental anomalies". After 157 to 167 days on test, F1 males were sacrificed and after 197 to 208 days, F1 females were sacrificed. Gross and histological examinations were performed on all F1 parents. Five randomly selected male and 5 female F1a progeny in each dose group were also examined histologically.

No compound related effect on parental body weight was observed. Food consumption was not effected by treatment in the F0 generation, but was significantly reduced for the F1 30 ppm females at week 16, 300 ppm females at weeks 6, 7, and 10 and the 1000 females at weeks 1, 6, 7, 8, 10, 13, 13, and 15, as compared to controls. Clinical observations of parental rats indicated no treatment-related effects. Pup survival was likewise not effected by treatment. Pup body weights of the 1000 ppm dose group were significantly reduced for F1a litters on days 14 and 21 and on days 4, 7, 14, and 21 for the F2a litters. Pup body weights of the 30 and 300 ppm dose groups did not appear to be effected in a compound-related manner. Liver-to-body weight ratios were significantly increased for both F1 parental males and females at 1000 ppm. The thyroid-to-body weight ratio and thyroid-to-brain weight ratio of 1000 ppm F1 males were significantly increased. Body weights of the weanling 1000 ppm F1a females and F2a males were reduced, though not significantly, and body weights of F2a weanling females were significantly reduced. The NOEL and LEL for reproductive toxicity are 300 and 1000 ppm (15 and 50 mg/kg/day), respectively, based on reduced pup weights and reduced parental food consumption.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The UF of 100 allows for uncertainty in the extrapolation of dose levels from laboratory animals to humans (10A) and uncertainty in the threshold for sensitive humans (10H).

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Data Considered for Establishing the RfD

1) 2-Year Feeding (oncogenic) - rat: Principal study - see previous description; core grade minimum (Ciba-Geigy Corp., 1983)

2) 2-Generation Reproduction - rat: Co-Principal study - see previous description; core grade guideline (Ciba-Geigy Corp., 1981)

3) Teratology - rat: Maternal, Fetotoxic, and Teratogenic NOEL=360 mg/kg/day (HDT); Maternal, Fetotoxic, and Teratogenic LEL=none; core grade minimum (Ciba-Geigy Corp., 1976)

4) Teratology - rabbit: Maternal NOEL=120 mg/kg/day; Maternal LEL=none; Fetotoxic and Teratogenic NOEL=360 mg/kg/day; Fetotoxic and Teratogenic LEL=none; core grade minimum (Ciba-Geigy Corp., 1980)

Other Data Reviewed:

1) 2-Year Feeding (oncogenic) - mice: Systemic NOEL=1000 ppm (150 mg/kg/day); Systemic LEL=3000 ppm (450 mg/kg/day); core grade minimum (Ciba-Geigy Corp., 1982)

Data Gap(s): 6-Month Dog Study is under review

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — High
RfD — High

Both co-critical studies are of good quality and are jointly given a medium confidence rating. Additional studies are supportive and of good quality; therefore, the database is given a high confidence rating. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Pesticide Registration Standard, September 1980

Pesticide Registration Files

Agency Work Group Review — 04/22/1986, 05/25/1988, 06/22/1988, 12/14/1993

Verification Date — 06/22/1988

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name —Metolachlor
CASRN — 51218-45-2

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name —Metolachlor
CASRN — 51218-45-2
Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document.

IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen.

Basis — Classification is based on the appearance of proliferative liver lesions (combined neoplastic nodules and carcinomas) at highest dose tested (3000 ppm) in female rats.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Limited. Two chronic rat studies were conducted wherein metolachlor was incorporated in the diet for 2 years. Industrial Biotest Laboratories (IBT, 1979) fed 0, 30, 300, 1000, and 3000 ppm of metolachlor in the diet to 60 Charles River strain albino rats/sex/group. Proliferative hepatic lesions were significantly increased only in high-dose females when hyperplastic or neoplastic nodules were combined with angiosarcomas, cystic cholangiomas, cholangiomas and carcinomas. Inadequacies of this study, such as incomplete hematology, urinalysis, clinical chemistry, and dietary preparation records, prompted a repeat of the study.

Hazelton-Raltech, Inc. (1983) administered 0, 30, 300, or 3000 ppm metolachlor to 60-70 Charles River CD rats/sex/group for 104 weeks. There was a statistically significant increase in liver neoplastic nodules and carcinomas in the high-dose females when compared to controls. The increase was largely due to the occurrence of neoplastic nodules. No statistically significant increase in liver tumors was observed in male rats in either study.

Two chronic (2-year) mouse studies (IBT, 1977; Hazelton-Raltech, 1982) were conducted in which metolachlor was incorporated into the diet. IBT (1977) administered metolachlor at 0, 30, or 300 ppm; Halzelton-Raltech (1982) administered the compound at 300, 1000, or 3000 ppm. There were no oncogenic effects ($p>0.05$) noted in either study. The high dose produced weight reduction, thereby indicating that an MTD had been reached.

II.A.4. Supporting Data for Carcinogenicity

Metolachlor was not mutagenic in reverse mutation assays in Salmonella (U.S. EPA, 1985). Its structure is similar to alachlor, which has been classified B2, but alachlor produces oncogenic response at different tumor sites (alachlor produces nasal turbinate, stomach and thyroid tumors). Available metabolic data indicate that both metolachlor and alachlor are metabolized to aniline derivatives (U.S. EPA, 1985).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1985

The Toxicology Branch Peer Review Committee Office of Pesticide Programs, Office of Pesticides and Toxic Substances reviewed data on metolachlor.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 11/10/1987

Verification Date — 11/10/1987

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name —Metolachlor
CASRN — 51218-45-2

VI.A. Oral RfD References

Ciba-Geigy Corporation. 1976. MRID No. 00015396. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1980. MRID No. 00041283. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1981. MRID No. 00080897. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1982. MRID No. 00039194, 00117597. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1983. MRID No. 00063398, 00084005, 00129377, 00144364, 00158924. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

Hazelton-Raltech, Inc. 1982. Carcinogenicity Study with Metolachlor in Albino Mice. Cited in U.S. EPA, 1985.

Hazelton-Raltech, Inc. 1983. Chronic Rat Study of Metolachlor. Cited in U.S. EPA, 1985.

IBT (Industrial Biotest Laboratories). 1977. Oncogenic Mice. Cited in U.S. EPA, 1985.

IBT (Industrial Biotest Laboratories). 1979. Two-year Chronic Oncogenicity Oral Toxicity Study with Metolachlor in Albino Rats. Cited in U.S. EPA, 1985.

U.S. EPA. 1985. Toxicology Branch Peer Review Committee, Office of Pesticide Programs, Office of Pesticides and Toxic Substances memorandum on metolachlor. May 30.

VII. Revision History

Substance Name —Metolachlor
CASRN — 51218-45-2

Date	Section	Description
06/30/1988	I.A.	Withdrawn pending further review
08/22/1988	II.	Carcinogen summary on-line
09/07/1988	I.A.	Revised oral RfD summary added
10/01/1990	I.A.1.	Oral RfD corrected

VIII. Synonyms

Substance Name —Metolachlor
CASRN — 51218-45-2
Last Revised — 01/31/1987

- 51218-45-2
- ACETAMIDE, 2-CHLORO-N-(6-ETHYL-o-TOLYL)-N-(2-METHOXY-1-METHYLETHYL)-
- o-ACETOTOLUIDIDE, 2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)-
- 2-AETHYL-6-METHYL-N-(1-METHYL-2-METHOXYAETHYL)-CHLORACETANILID
- BICEP
- CGA-24705
- alpha-CHLOR-6'-AETHYL-n-(2-METHOXY-1-METHYLAETHYL)-ACET-o-TOLUIDIN
- alpha-CHLORO-2'-ETHYL-6'-METHYL-N-(1-METHYL-2-METHOXYETHYL)-ACETANILIDE
- 2-CHLORO-6'-ETHYL-N-(2-METHOXY-1-METHYLETHYL)ACET-o-TOLUIDIDE
- 2-CHLORO-N-(2-ETHYL-6-METHYLPHENYL)-N-(2-METHOXY-1-METHYLETHYL)ACETAMIDE
- CODAL
- COTORAN MULTI
- DUAL
- 2-ETHYL-6-METHYL-1-N-(2-METHOXY-1-METHYLETHYL)CHLOROACETANILIDE
- METELILACHLOR
- Metolachlor
- MILOCEP
- ONTRACK 8E
- PRIMAGRAM
- PRIMEXTRA

Attachment C

USEPA Office of Chemical Safety and Pollution Prevention
Metolachlor and S-Metolachlor: Draft Human Health Risk Assessment for Registration Review

August 8, 2023

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 12, 2019

SUBJECT: Metolachlor and S-Metolachlor: Draft Human Health Risk Assessment for Registration Review

PC Code: 108800 S-metolachlor; 108801 Metolachlor	**DP Barcode:** D452047
Decision No.: 550679	**Registration No.:** Multiple
Petition No.: NA	**Regulatory Action:** Registration Review
Risk Assessment Type: Single Chemical/Aggregate	**Case No.:** 0001
TXR No.: NA	**CAS No.:** 87392-12-9; 51218-45-2
MRID No.: NA	**40 CFR:** §180.368

FROM: Jessica Kidwell, Toxicologist/Risk Assessor
Brian Van Deusen, Occupational/Residential Exposure Assessor
Shirley Keel, Dietary Exposure Assessor/Residue Chemist
Risk Assessment Branch 4 (RAB4)
Health Effects Division (HED) (7509P)

THROUGH: Kristin Rickard, Acting Branch Chief
RAB4/HED (7509P)

TO: Ana Pinto, Chemical Review Manager
Avivah Jakob, Team Leader
Kelly Sherman, Branch Chief
Risk Management and Implementation Branch III (RMIB III)
Pesticide Re-Evaluation Division (PRD) (7508P)

PRD has requested that HED conduct a draft human health risk assessment for metolachlor and S-metolachlor for Registration Review. To address this request, HED has relied on the 2018 S-metolachlor risk assessment (Kidwell, J., *et al*., 9/27/2018, D447125) for hazard characterization and endpoint selection, as well as for the dietary exposure assessment. The endpoints for metolachlor/S-metolachlor were updated in the 2018 assessment. Drinking water estimates are the same as those assessed in the 2018 assessment, so dietary analyses are the same. The existing registered residential uses for S-metalochlor were assessed in 2018 and remain unchanged for this assessment. For this draft risk assessment (DRA) action, an updated occupational assessment was completed to evaluate the existing uses of metolachlor and S-metolachlor to reflect recent updates to HED's SOPs/policies. A summary of the findings and an assessment of risk resulting from the registered uses of metolachlor and S-metolachlor are provided in this document.

Table of Contents

1.0 Executive Summary

Background and Use Pattern
Metolachlor (PC Code 108801) is a racemic herbicide that consists of 50% each of the R-enantiomer and the S-enantiomer, which is the herbicidally active isomer. S-metolachlor (PC Code 108800) is an isomer enriched form of metolachlor, comprised of 88% S-enantiomer and 12% R-enantiomer. Metolachlor and S-metolachlor are selective, chloroacetanilide herbicides used primarily for grassy weed control in many agricultural food and feed crops. S-metolachlor is used by commercial handlers on residential lawns; commercial turf (including golf courses, sports fields, recreation areas, and sod farms); field- and container-grown ornamental plants, trees, shrubs, and vines; hedge rows; and horticultural nurseries.

Exposure Profile
Humans may be exposed to metolachlor and S-metolachlor in food and drinking water since they may be applied directly to growing crops and following harvest, and application may result in both chemicals reaching surface and ground sources of drinking water. In an occupational setting, applicators may be exposed (dermal and inhalation) while handling the herbicides prior to application, as well as during application. There is also potential for post-application exposure for workers (dermal) re-entering treated fields and contacting treated commodities. In a residential setting, adults (dermal) and children (dermal and incidental oral) may be exposed following application of S-metolachlor in residential areas (i.e., residential turfgrass, golf courses, recreation areas, etc.). There is also the potential for non-occupational exposure resulting from spray drift from agricultural applications onto residential areas from both metolachlor and S-metolachlor.

Hazard Characterization
The existing toxicological database is comprised of studies conducted with both metolachlor and S-metolachlor. The Agency has concluded that it is appropriate to bridge the two chemicals such that the metolachlor toxicology database can be used to assess toxicity for S-metolachlor and *vice versa*. The toxicology database for S-metolachlor, when combined with the metolachlor database, is complete for risk assessment purposes. Although the neurotoxicity battery (870.6200 a and b) is required in accordance with the revised 40 CFR Part 158 Toxicology Data Requirements, the data requirement for the neurotoxicity studies was recommended for a waiver by the Hazard and Science Policy Council (HASPOC) in 2013. The HASPOC also recommended that a subchronic inhalation study with metolachlor is required. Subsequently, this study has been submitted, reviewed and found to be acceptable. The 10X data base uncertainty factor, which was previously applied only for assessing risk for inhalation scenarios, was removed.

In subchronic (metolachlor and S-metolachlor) and chronic (metolachlor) toxicity studies in dogs, rats and mice, decreased body weight was the most commonly observed treatment-related effects. Chronic exposure to metolachlor in rats also resulted in increased liver weight and microscopic liver lesions (foci of cellular alteration) in both sexes. There was no evidence of systemic toxicity at the limit dose in a 21-day dermal toxicity metolachlor study in rabbits, however, dermal irritation was observed at lower doses. There was no evidence of systemic toxicity at the limit dose in a 28-day inhalation study in rats with metolachlor, although portal of

entry effects occurred in the nasal cavity at lower doses. These effects included hyperplasia of the squamous epithelium and subacute inflammation and mucous cell hyperplasia. There was no evidence of immunotoxicity in mice with S-metolachlor.

There was no evidence of a mutagenic or cytogenetic effect *in vivo* or *in vitro* in studies with either metolachlor or S-metolachlor. For metolachlor, there was no evidence of carcinogenicity in mice or male rats; however, there were treatment-related liver tumors in female rats in the chronic toxicity/carcinogenicity study. A mitogenic mode of action was accepted for these tumors.

There was no evidence of increased quantitative or qualitative fetal susceptibility in the prenatal developmental studies in rats and rabbits with either metolachlor or S-metolachlor. No developmental toxicity was seen in rats or rabbits with metolachlor and S-metolachlor. In the rat developmental toxicity study with metolachlor, death and clinical signs (clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur) were observed at the limit dose in maternal animals in the absence of developmental effects. In the S-metolachlor rabbit developmental toxicity study, clinical signs of toxicity (little/none/soft stool) were observed in maternal animals in the absence of developmental effects. In the two-generation reproduction study in rats conducted with metolachlor, there was quantitative evidence of susceptibility. Decreased pup body weight in F1 and F2 litters was seen in the absence of maternal toxicity.

The acute toxicity battery of studies for metolachlor showed that it exhibits low acute toxicity via the oral (Toxicity Category III), dermal (Toxicity Category IV), and inhalation (Toxicity Category IV) routes of exposure. It is slightly irritating to the eyes (Toxicity Category III) minimally irritation to the skin (Toxicity Category IV) and is a dermal sensitizer.

The acute toxicity battery of studies for S-metolachlor showed that it exhibits low acute toxicity via the oral (Toxicity Category III), inhalation (Toxicity Category IV), and dermal (Toxicity Category III) routes of exposure. It causes slight to moderate eye irritation (Toxicity Category III), is non-irritating to the skin (Toxicity Category IV) but is a dermal sensitizer.

Endpoints and Uncertainty Factors
Toxicological endpoints were selected for chronic dietary (food + drinking water), residential, and occupational exposure scenarios. Since quantitative susceptibility (i.e., decreased pup body weight occurred in the absence of maternal toxicity) was seen in the two-generation reproduction toxicity study in rats with metolachlor, this study was selected for several endpoints, including the chronic dietary (all populations) as well as the dermal and incidental oral scenarios for children. The point of departure (POD) used was the offspring no observed adverse effect level (NOAEL) of 26 mg/kg/day based on decreased pup body weight in F1 and F2 litters observed at the offspring lowest observed adverse effect level (LOAEL) of 86 mg/kg/day. For dietary exposure, the chronic reference dose (cRfD) (equivalent to the chronic population adjusted dose (cPAD)) was 0.26 mg/kg/day. An acute dietary assessment for all populations is not required since there is no applicable endpoint attributable to a single dose. For the dermal and incidental oral exposure scenarios for children, the POD is the offspring NOAEL = 26 mg/kg/day. The residential level of concern (LOC) for the margin of exposure is 100 (10X interspecies extrapolation, 10X intraspecies variation, and 1X Food Quality Protection Act (FQPA) Safety

Factor (SF)). For adults, a dermal assessment is not required since no systemic effects were seen up to the limit dose of 1000 mg/kg/day in a 21-day dermal toxicity study in rabbits with metolachlor and the quantitative susceptibility seen in the offspring in the 2-generation reproduction study is not relevant for adults. The short-and intermediate-term inhalation POD was selected for all populations from a route-specific 28-day inhalation toxicity study in rats with metolachlor. A portal of entry no-observed adverse effect concentration (NOAEC) of 0.1 mg/L (equivalent to 100 mg/m^3) and a portal of entry lowest-observed-adverse-effect-concentration (LOAEC) of 0.3 mg/L (300 mg/m^3) were identified based on hyperplasia of the squamous epithelium and subacute inflammation in both sexes, and mucous cell hyperplasia in males at nasal level II. This route specific study is appropriate for the duration and population of concern (all populations). The portal of entry effects provide a lower POD (Human Equivalent Doses) than the two-generation reproduction study and is, therefore, protective of quantitative susceptibility seen in that study. The occupational inhalation level of concern is 30X (3X for interspecies extrapolation, 10X for intraspecies variation, FQPA SF 1X).

Dietary Exposure
For the Registration Review of metolachlor and its registered active isomer, S-metolachlor, the Environmental Fate and Effects Division (EFED) updated the estimated drinking water concentrations (EDWCs) with the available new environmental fate data using the Pesticide Water Calculator (PWC) (Antoline, J., 10/31/2018, D448964). The maximum chronic EDWC **decreased** from the previous value of 978 ug/L to 830 ug/L (based on groundwater modeling). Subsequently, EFED incorporated the SLN (Special Local Needs) max use rate, which did not result in any changes in the updated EDWCs. Therefore, the maximum chronic EDWC remains 830 ug/L for groundwater (e-mail communication between G. Orrick and A. Jakob, 9/4/2019). With no new uses since the most recent risk assessment (Kidwell, J. *et al*., 9/27/2018, D447125) and a lower updated EDWC, the risk estimates of food and drinking water for metolachlor/S-metolachlor of the previous 2018 dietary assessment (Keel¸ S., 9/17/2018, D447126) continue to be applicable for Registration Review.

The 2018 chronic dietary (food and drinking water) exposure analysis for metolachlor/ S-metolachlor was unrefined. The analysis assumed 100% crop treated and incorporated tolerance-level residues, default processing factors, and the model-derived maximum EDWC for all direct and indirect water sources provided by EFED. The resulting chronic risk estimates of food and drinking water for metolachlor/S-metolachlor are below the Agency's level of concern [<100% of the cPAD] for the general U.S. population and all population subgroups. The most highly exposed subgroup is "all infants <1 year old" with a risk estimate at 22% of the cPAD, whereas the risk estimate for the general US population is at 8.7% of the cPAD.

Residential Exposures and Risks
There are no existing registered residential uses of metolachlor.

There are existing registered residential uses for S-metolachlor that were previously assessed (Van Deusen, B., 9/25/2018, D447124) on residential warm-season turf grasses, and other non-crop land including golf courses, sports fields, parks, lawns, and ornamental gardens that would result in residential post-application exposures. A summary of the exposures and risks associated with the registered residential uses that were recommended for use in the aggregate risk

assessment for S-metolachlor are provided. Since no adult dermal hazard was identified, a quantitative dermal assessment was not conducted for adult residential post-application scenarios. However, the registered uses of S-metolachlor are expected to result in residential post-application exposure for children via the dermal and incidental oral routes of exposure and these uses were quantitatively assessed. All residential post-application exposures resulted in no risks of concern (i.e., MOEs are ≥100, ranging from 120 to 670,000).

Available chemical-specific turf transferable residue (TTR) data were used for assessment of residential exposures. Since dislodgeable foliar residue (DFR) data were not available, default exposure data were used for assessment of post-application exposures to treated gardens and incorporated a time-weighted average residue rather than a repeated daily "day 0" residue point estimate that does not account for dissipation.

Aggregate Risk Assessment
There is no applicable endpoint attributable to a single dose, so there is not acute point of departure and acute dietary and aggregate risk assessments are not required. The chronic aggregate risk assessment considers exposure estimates from dietary (food + drinking water) consumption of metolachlor/S-metolachlor. As referenced above, the chronic dietary risk estimates are not of concern to HED (<100% cRfD). In aggregating short-term risk, the Agency routinely combines background chronic dietary (food + drinking water) exposure with short-term residential exposures. The combined exposure may then be used to calculate an MOE for aggregate risk. Using the post application exposures (for children via the dermal and/or incidental oral routes of exposure) from contact with treated turf and/or lawns, combined with the applicable subpopulation dietary exposures, the short-term residential aggregate MOEs ranged from 110-1,200. As these MOEs exceed 100, the short-term aggregate risks are not of concern.

Occupational Handler Exposures and Risks
There is the potential for occupational exposure from the registered uses of metolachlor and S-metolachlor. For the occupational handler assessment, a screening-level approach was used which combined registered crops into surrogate groups and assessed the maximum application rate per group to assess all potential exposure scenarios. Since no adult occupational dermal hazard was identified, a quantitative dermal assessment was not conducted for the occupational uses. All inhalation risk estimates for occupational handlers of metolachlor and S-metolachlor are not of concern (i.e., MOE ≥ 30) with engineering controls or baseline attire and no respirator.

Occupational Post-Application Exposures and Risks
Occupational post-application dermal exposure and risk estimates were not assessed since an adult occupational dermal hazard was not identified. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for metolachlor/S-metolachlor at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for metolachlor/S-metolachlor.

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1, the AHETF database, the ORETF database, HED's 2012 Residential SOPs (Lawns/Turf and Gardens/Trees), and a registrant-submitted exposure monitoring study (MRID 44339801), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[1].

2.0 Risk Assessment Conclusions

The specific tolerance recommendations are discussed in Section 2.2, and label modifications are discussed in Section 2.3.

2.1 Data Deficiencies

Residue Chemistry: The analytical reference standard for CGA-37913 has expired and should be resubmitted. The standard for S-metolachlor (CGA-77102) will expire in fall of this year. HED recommends that the standard for S-metolachlor should also be resubmitted. Table 2.1.1 below indicates the status of analytical standards for the compounds related to metolachlor in the EPA National Pesticide Standards Repository (NPSR; e-mail communication between T. Cole and S. Keel, 7/24/2019). For the submission of analytical standards, please see Appendix C.

Table 2.1.1 Status of Analytical Standards

Chemical Name	Notes	Date of Expiration
Metolachlor		9/30/2027
metolachlor metabolite (CGA-37913)	**Out of Stock**	
metolachlor metabolite (CGA-49751)		1/31/2021
metolachlor, S- (CGA-77102)		**10/31/2019**

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Enforcement methods: Adequate methodology is available for enforcing the established and recommended tolerances. PAM Vol. II, Pesticide Regulation Section 180.368, lists a gas chromatography with nitrogen phosphorus detector (GC/NPD) method (Method I) for determining residues in/on crop commodities and a gas chromatography with mass selective detector (GC/MSD) method (Method II) for determining residues in livestock commodities. These methods determine residues of metolachlor and its metabolites as either CGA-37913 or CGA-49751 following acid hydrolysis (LOQs of 0.03 ppm and 0.05 ppm, respectively).

[1] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

2.2.2 Recommended & Established Tolerances

Tolerances for metolachlor residues are currently established in 40 CFR §180.368(a)(1) and (d)(1) for the combined residues (free and bound) of metolachlor and its metabolites, determined as the derivatives, CGA-37913 and CGA-47951, each expressed as the parent compound. Tolerances for S-metolachlor are currently established in 40 CFR §180.368(a)(2) and (d)(2) for the combined residues (free and bound) of S-metolachlor, its R-enantiomer, and its metabolites, determined as the derivatives, CGA-37913 and CGA-47951, each expressed as the parent compound. A summary of recommended tolerance revisions for metolachlor and S-metolachlor are listed in the Table 2.2.2.1 and Table 2.2.2.2, respectively.

TABLE 2.2.2.1 Tolerance Revision for Metolachlor (40CFR §180.368(a)(1)).

Commodity/**Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance[1] (ppm)	Comments
Almond, hulls	-	**0.3**	Corrected values to be consistent with OECD Rounding Class Practice.
Almond, hulls	0.30	Remove	
Animal feed, nongrass, group 18	-	**1**	
Animal feed, nongrass, group 18	1.0	Remove	
Cattle, kidney	-	**0.2**	
Cattle, kidney	0.20	Remove	
Corn, field, forage	-	**6**	
Corn, field, forage	6.0	Remove	
Corn, field, grain	-	**0.1**	
Corn, field, grain	0.10	Remove	
Corn, field, stover	-	**6**	
Corn, field, stover	6.0	Remove	
Corn, pop, grain	-	**0.1**	
Corn, pop, grain	0.10	Remove	
Corn, pop, stover	-	**6**	
Corn, pop, stover	6.0	Remove	
Corn, sweet, forage	-	**6**	
Corn, sweet, forage	6.0	Remove	
Corn, sweet, kernel plus cob with husks removed	-	**0.1**	
Corn, sweet, kernel plus cob with husks removed	0.10	Remove	
Corn, sweet, stover	-	**6**	
Corn, sweet, stover	6.0	Remove	
Cotton, gin byproducts	-	**4**	
Cotton, gin byproducts	4.0	Remove	
Cotton, undelinted seed	-	**0.1**	
Cotton, undelinted seed	0.10	Remove	
Dillweed	-	**0.5**	
Dillweed	0.50	Remove	
Goat, kidney	-	**0.2**	
Goat, kidney	0.20	Remove	
Grass, hay	-	**0.2**	
Grass, hay	0.20	Remove	
Horse, kidney	-	**0.2**	

TABLE 2.2.2.1 Tolerance Revision for Metolachlor (40CFR §180.368(a)(1)).			
Commodity/**Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance[1] (ppm)	Comments
Horse, kidney	0.20	Remove	
Nut, tree, group 14	-	**0.1**	
Nut, tree, group 14	0.10	Remove	
Okra	-	**0.5**	
Okra	0.50	Remove	
Peanut	-	**0.2**	
Peanut	0.20	Remove	
Peanut, meal	-	**0.4**	
Peanut, meal	0.40	Remove	
Potato	-	**0.2**	
Potato	0.20	Remove	
Safflower, seed	-	**0.1**	
Safflower, seed	0.10	Remove	
Sheep, kidney	-	**0.2**	
Sheep, kidney	0.20	Remove	
Sorghum, grain, forage	-	**1**	
Sorghum, grain, forage	1.0	Remove	
Sorghum, grain, grain	-	**0.3**	
Sorghum, grain, grain	0.30	Remove	
Sorghum, grain, stover	-	**4**	
Sorghum, grain, stover	4.0	Remove	
Soybean, forage	-	**5**	
Soybean, forage	5.0	Remove	
Soybean, hay	-	**8**	
Soybean, hay	8.0	Remove	
Soybean, seed	-	**0.2**	
Soybean, seed	0.20	Remove	
Tomato	-	**0.1**	
Tomato	0.10	Remove	
Vegetable, foliage of legume, subgroup 7A, except soybean	-	**15**	
Vegetable, foliage of legume, subgroup 7A, except soybean	15.0	Remove	
Vegetable, legume, group 6	-	**0.3**	
Vegetable, legume, group 6	0.30	Remove	

[1] Tolerance level as recommended by HED.

TABLE 2.2.2.2 Tolerance Revision for S-Metolachlor (40CFR §180.368(a)(2)).			
Commodity/**Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance[1] (ppm)	Comments
Beet, sugar, leaves	-	**15**	- Commodity definition revision.
Beet, sugar, tops	15.0	Remove	- Corrected values to be consistent with OECD Rounding Class Practice.
Beet, sugar, molasses	-	**2**	Corrected values to be consistent with OECD Rounding Class Practice.
Beet, sugar, molasses	2.0	Remove	
Berry, low growing, subgroup 13-07G, except cranberry	-	**0.4**	- Commodity definition revision.

TABLE 2.2.2.2 Tolerance Revision for S-Metolachlor (40CFR §180.368(a)(2)).			
Commodity/**Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance[1] (ppm)	Comments
Low growing berry subgroup 13-07G, except cranberry	0.40	Remove	- Corrected values to be consistent with OECD Rounding Class Practice
Brassica, leafy greens, subgroup 4-16B	-	1.8	Commodity definition revision.
Brassica, leafy greens, subgroup 4-16 B	1.8	-	
Caneberry subgroup 13-07A	-	**0.1**	Corrected values to be consistent with OECD Rounding Class Practice.
Caneberry subgroup 13-07A	0.10	Remove	
Carrot, roots	-	**0.4**	
Carrot, roots	0.40	Remove	
Cattle, kidney	-	**0.2**	
Cattle, kidney	0.20	Remove	
Cilantro, leaves	-	**8**	
Cilantro, leaves	8.0	Remove	
Corn, field, grain	-	**0.1**	
Corn, field, grain	0.10	Remove	
Corn, pop, grain	-	**0.1**	
Corn, pop, grain	0.10	Remove	
Corn, sweet, kernel plus cob with husks removed	-	**0.1**	
Corn, sweet, kernel plus cob with husks removed	0.10	Remove	
Cotton, gin byproducts	-	**4**	
Cotton, gin byproducts	4.0	Remove	
Cottonseed subgroup 20C	-	**0.1**	
Cottonseed subgroup 20C	0.10	Remove	
Grain, aspirated fractions	-	**0.7**	
Grain, aspirated fractions	0.70	Remove	
Goat, kidney	-	**0.2**	
Goat, kidney	0.20	Remove	
Grass, forage	-	**10**	
Grass, forage	10.0	Remove	
Grass, hay	-	**0.2**	
Grass, hay	0.20	Remove	
Horse, kidney	-	**0.2**	
Horse, kidney	0.20	Remove	
Kohlrabi	-	**0.6**	
Kohlrabi	0.60	Remove	
Leaf petiole vegetable subgroup 22B	-	**0.1**	
Leaf petiole vegetable subgroup 22B	0.10	Remove	
Onion, bulb, subgroup 3-07A	-	**0.1**	
Onion, bulb, subgroup 3-07A	0.10	Remove	
Onion, green, subgroup 3-07B	-	**2**	
Onion, green, subgroup 3-07B	2.0	Remove	
Peanut	-	**0.2**	
Peanut	0.20	Remove	
Peanut, hay	-	**20**	
Peanut, hay	20.0	Remove	
Peanut, meal	-	**0.4**	

TABLE 2.2.2.2 Tolerance Revision for S-Metolachlor (40CFR §180.368(a)(2)).			
Commodity/**Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance[1] (ppm)	Comments
Peanut, meal	0.40	Remove	
Safflower, seed	-	**0.1**	
Safflower, seed	0.10	Remove	
Sheep, kidney	-	**0.2**	
Sheep, kidney	0.20	Remove	
Sorghum, grain, forage	-	**1**	
Sorghum, grain, forage	1.0	Remove	
Sorghum, grain, stover	-	**4**	
Sorghum, grain, stover	4.0	Remove	
Sorghum, sweet, stalk	-	**4**	
Sorghum, sweet, stalk	4.0	Remove	
Soybean, forage	-	**5**	
Soybean, forage	5.0	Remove	
Soybean, hay	-	**8**	
Soybean, hay	8.0	Remove	
Soybean, seed	-	**0.2**	
Soybean, seed	0.20	Remove	
Spinach	-	**0.5**	
Spinach	0.50	Remove	
Stalk and stem vegetable subgroup 22A, except kohlrabi	-	**0.1**	
Stalk and stem vegetable subgroup 22A, except kohlrabi	0.10	Remove	
Sugarcane, cane	-	**0.2**	
Sugarcane, cane	0.20	Remove	
Sunflower, meal	-	**1**	
Sunflower, meal	1.0	Remove	
Sunflower subgroup 20B	-	**1**	
Sunflower subgroup 20B	1.0	Remove	
Tomato, paste	-	**0.3**	
Tomato, paste	0.30	Remove	
Vegetable, Brassica, head and stem, group 5-16	-	**0.6**	- Commodity definition revision. - Corrected values to be consistent with OECD Rounding Class Practice.
Vegetable, *Brassica*, head and stem, group 5-16	0.60	Remove	
Vegetable, cucurbit group 9	-	**0.5**	
Vegetable, cucurbit group 9	0.50	Remove	
Vegetable, foliage of legume, except soybean, subgroup 7A	-	**15**	
Vegetable, foliage of legume, except soybean, subgroup 7A	15.0	Remove	Corrected values to be consistent with OECD Rounding Class Practice.
Vegetable, fruiting, group 8-10, except tabasco pepper	-	**0.1**	
Vegetable, fruiting, group 8-10, except tabasco pepper	0.10	Remove	
Vegetable, leaves of root and tuber, group 2, except sugar beet	-	**2**	

TABLE 2.2.2.2 Tolerance Revision for S-Metolachlor (40CFR §180.368(a)(2)).			
Commodity/**Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance[1] (ppm)	Comments
Vegetable, leaves of root and tuber, group 2, except sugar beet	2.0	Remove	
Vegetable, legume, group 6	-	**0.3**	
Vegetable, legume, group 6	0.30	Remove	
Vegetable, root, except sugar beet, subgroup 1B, except carrot	-	**0.3**	
Vegetable, root, except sugar beet, subgroup 1B, except carrot	0.30	Remove	
Vegetable, tuberous and corm, subgroup 1C	-	**0.2**	
Vegetable, tuberous and corm, subgroup 1C	0.20	Remove	

[1] Tolerance level as recommended by HED.

2.2.3 International Harmonization

No maximum residue limits (MRLs) for metolachlor or S-metolachlor have been established or proposed by Codex. Mexico adopts US tolerances and/or Codex MRLs for its export purposes. The US tolerance definition for S-metolachlor is harmonized with Canada. No MRLs for metolachlor have been established in Canada, although Canada has established numerous MRLs for S-metolachlor in/on crop commodities, which have been harmonized with established U.S. tolerances. These include individual commodities (carrot root, corn, egg, poultry meat and meat byproducts, livestock meat, cattle kidney and liver, milk and peanut), and members of many crop groups/subgroups—bushberry subgroup 13-07B, leaf petiole vegetable subgroup 22B, cucurbit vegetable group 9, fruiting vegetable group 8-10, legume vegetable group 6 (except dry soybean), root vegetable (except sugar beet) subgroup 1B (except parsnip root and rutabaga roots), stalk and stem vegetable subgroup 22A, and tuberous and corm vegetable subgroup 1C.

The Canadian MRLs in/on the following crop commodities— sugar beet root (Canada 0.3 ppm vs. US 0.5 ppm), strawberry (Canada 0.1 ppm vs. US 0.4 ppm), dry soybean (Canada 0.2 ppm vs. US 0.3 ppm), rutabaga roots (Canada 0.1 ppm vs. US 0.3 ppm), and members of brassica leafy greens subgroup 4-16B (Canada 0.9 vs. US 1.8 ppm) and leaves of root and tuber vegetable group 2 (Canada 0.8 vs. US 2 ppm)—are too low to harmonize with established US tolerances. Canada has established the MRL for residues of S-metolachlor in/on apple, pear, meat of hog, and stone fruits (apricot, cherry, nectarine, peach and plum) for which there are no U.S. equivalents. See Appendix D, International Residue Limit Status Sheet, for more details.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

Label revisions recommended by HED (Kidwell, J. *et al*, 9/27/2018, D447125) for EPA Registration No. 100-816 are still outstanding.

2.3.2 Recommendations from Residential Assessment

None.

2.3.3 Recommendations from Occupational Exposure Assessment

None.

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature of metolachlor and S-metolachlor and its regulated hydrolytic derivatives are presented in Table 3.1.1

Table 3.1.1 Nomenclature of Metolachlor and S-metolachlor and Regulated Hydrolytic Derivatives.

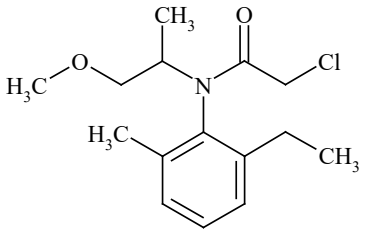
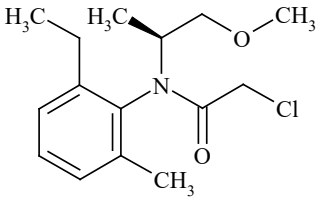
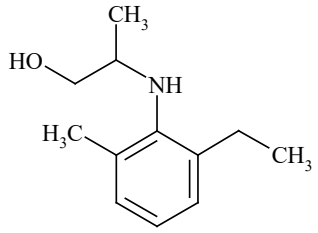
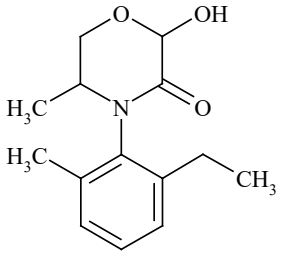
Parent compound	
Common name	Metolachlor
Company experimental name	CGA-24705
IUPAC name	2-chloro-*N*-(6-ethyl-*o*-tolyl)-*N*-[(1*RS*)-2-methoxy-1-methylethyl]acetamide or (*aRS*,1*RS*)-2-chloro-6′-ethyl-*N*-(2-methoxy-1-methylethyl)acet-*o*-toluidide
CAS name	2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-(2-methoxy-1-methylethyl)acetamide
CAS registry number	51218-45-2
Chemical formula	$C_{15}H_{22}ClNO_2$
Parent compound	
Common name	2S-metolachlor
Company experimental name	CGA-77102
IUPAC name	(S)-2-chloro-N-(2-ethyl-6-methyl-phenyl)-N-(2-metonym-1-methyl-ethyl)-acetamide
CAS name	2-chloro-N-(2-ethyl-6-methylphenyl)-N-[(1S)2-methoxy-1-methylethyl]-acetamide
CAS registry number	87392-12-9
Chemical formula	$C_{15}H_{22}ClNO_2$

Table 3.1.1 Nomenclature of Metolachlor and S-metolachlor and Regulated Hydrolytic Derivatives.	
Regulated residue	
Common name	None
Company experimental names	CGA-37913 SYN506357 (S-enantiomer of CGA 37913)
Chemical name	2-[(2-ethyl-6-methylphenyl) amino]-1-propanol
CAS registry number	61520-53-4 82508-08-5 (S-enantiomer)
Regulated residue	
Common name	None
Company experimental names	CGA-49751 SYN508500 (S-enantiomer of CGA 49751)
Chemical name	4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone
CAS registry number	61520-54-5

3.2 Physical/Chemical Characteristics

Metolachlor is a racemic mixture of R-and S-enantiomers, whereas S-metolachlor is an enrichment of S-enantiomers with a higher portion of the more herbicidally active S-isomer (88%). Metolachlor and S-metolachlor have the same physical/chemical properties except for the direction in which they rotate polarized light. Both metolachlor and S-metolachlor are fairly soluble in water (0.48 g/L), and completely miscible with typical pesticide solvents. Both have a moderately low vapor pressure (2.8 x 10^{-5} mm Hg). Both do not dissociate and have a high octanol-water partition coefficient (LogK_{OW}) = 3.0 at 25 C). Environmental fate data indicate that parent metolachlor/S-metolachlor is moderately persistent to persistent. Both are mobile to highly mobile in different soils and have been detected extensively in surface water and groundwater. Metolachlor/S-metolachlor degradation appears to be dependent on microbial mediated and abiotic processes. The physicochemical properties of metolachlor/S-metolachlor are presented in Table 3.2.1.

Table 3.2.1 Physicochemical Properties of Metolachlor/S-metolachlor.		
Parameter	Value	Reference
Melting point/range	Not applicable, liquid at room temperature	MRID 47121701 (McNeilly, D., 10/21/2008, D332846)
pH	7.8 at 25 ºC (1% aqueous dispersion)	
Density	1.117 g/cm^3 at 20 ºC	
Water solubility (25°C)	0.48 g/L	
Solvent solubility (mg/L at 25°C)	Completely miscible with methanol, acetone, toluene, n-octanol, n-hexane, ethyl acetate, and dichloromethane.	
Vapor pressure at 25°C	2.8 x 10^{-5} mm Hg	
Dissociation constant (pK_a)	No dissociation constant in pH range 2-12	
Octanol/water partition coefficient Log(K_{OW})	3.05 at 25 ºC	
UV/visible absorption spectrum	Neutral: 534 L/mol•cm @ 266.4 nm 443 L/mol•cm @ 274.4 nm Acidic: 534 L/mol•cm @ 266.4 nm 444 L/mol•cm @ 274.4 nm Basic: 531 L/mol•cm @ 266.4 nm 411 L/mol•cm @ 274.4 nm	

3.3 Pesticide Use Pattern

Metolachlor
Metolachlor is currently registered for several agricultural crops and may be applied as a preplant surface-applied, preplant incorporated, preemergence, postemergence, or postharvest treatment via aerial, ground, center-pivot irrigation equipment, or handheld spray equipment for control of most annual grasses, certain broadleaf weeds in beans, corn (field, pop, sweet), cotton, peanuts, peas, potato, safflower, sorghum, soybean, tomato, and for impregnation in dry bulk fertilizer.

Formulated products include a soluble concentrate (SC, EPA Reg. No. 60063-52) containing 58.2% metolachlor active ingredient (ai), and emulsifiable concentrates (ECs e.g., EPA Reg. No. 19713-548) containing up to 86.4% metolachlor ai. The maximum single application rates range from 2.67 to 2.75 lb ai/A. Registered labels require applicators and other handlers to wear coveralls over short- or long-sleeved shirt and short- or long pants, chemical resistant gloves, chemical resistant footwear plus socks, chemical resistant headgear for overhead exposure, and chemical resistant apron when cleaning equipment, mixing, or loading. Mixers and loaders supporting aerial applications are required to use closed systems. There are currently no metolachlor products registered for homeowner use and no products registered for application to residential areas. Preharvest intervals range from 30 to 120 days for all proposed use sites. The restricted entry interval (REI) on all section 3 registered labels is 24 hours while some Special Local Need (SLN) labels require a 12-hour REI.

S-Metolachlor
S-Metolachlor is currently registered for several agricultural crops and may be applied as a preplant surface-applied, preplant incorporated, preemergence, postemergence, or postharvest treatment via aerial, ground, center-pivot irrigation equipment, or handheld spray equipment for control of most annual grasses and certain broadleaf weeds in corn (sweet, field, and pop), cotton, potato, sugar beet, dry bean and pea, soybean, grasses grown for seed, peanut, safflower,

sorghum, sugarcane, sunflower, stevia (sunflower family), alfalfa, coriander, sesame, crop group 2 (sweet potato, radish, turnip, carrot, etc), horseradish, crop group 4-16B (arugula, kale, mustard greens, etc), crop group 5-16 (cabbage, broccoli, cauliflower etc), snap bean, chickpea, green pea, crop group 8-10 (bell pepper, tomato, eggplant, okra etc), crop group 9 (pumpkin, squash winter and summer, cucumber, etc), strawberry, crop group 22A (asparagus), crop group 22B (celery, rhubarb, etc), lettuce, leaf, head, swiss chard, crop group 3 bulb vegetables (onion, garlic), crop group 4-16A (spinach, swiss chard, lettuce leaf, leafy greens, parsley, etc), blackberry, blueberry, rasberry, nurseries, sod, forage (CRP), and for impregnation in dry bulk fertilizer.

Formulated products include a solid granule formulation (G, EPA Reg. No. 100-910) containing 16% S-metolachlor ai, emulsifiable concentrates (ECs e.g., EPA Reg. No. 100-816, 100-950, 100-1442, etc.), a flowable concentrate formulation (FlC, EPA Reg. No. 1381-199), soluble concentrates (SCs e.g., EPA Reg. No. IL140001), and as a liquid formulation for custom application to dry fertilizer (L, EPA Reg. No. 100-829) containing up to 83.7% S-metolachlor ai. The maximum single application rates range from 1.28 to 3.17 lb ai/A. All registered labels require occupational handlers to wear, at a minimum, baseline attire (long sleeved shirt, long pants, shoes, and socks), and waterproof and/or chemical resistant gloves. For certain activities/products, additional personal protective equipment (PPE) is required such as, coveralls and/or protective eyewear. There are currently no S-metolachlor products registered for homeowner use; however, there are registered uses for application to residential areas (turf, sod farms, landscape plantings/ornamentals, nurseries, and container grown plants). Preharvest intervals range from 16 to 120 days for all proposed use sites. The restricted entry interval (REI) on all registered labels is either 12 or 24 hours.

Tables E.1 and E.2 of Appendix E provide summaries of the registered uses of metolachlor and S-metolachlor, respectively.

3.4 Anticipated Exposure Pathways

Humans may be exposed to metolachlor and S-metolachlor in food and drinking water since they may be applied directly to growing crops and following harvest, and application may result in both chemicals reaching surface and ground sources of drinking water. In an occupational setting, applicators may be exposed (dermal and inhalation) while handling the herbicides prior to application, as well as during application. There is also potential for post-application exposure for workers (dermal) re-entering treated fields and contacting treated commodities. In a residential setting, adults (dermal) and children (dermal and incidental oral) may be exposed following application of S-metolachlor in residential areas (i.e., residential turfgrass, golf courses, recreation areas, etc.). There is also the potential for non-occupational exposure to both chemicals resulting from spray drift from agricultural applications onto residential areas.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations,"

(https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it is also being considered whenever appropriate. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The existing toxicological database is comprised primarily of studies conducted with metolachlor. The toxicology database for S-metolachlor consists of bridging data. Based on a comparison of findings in the two databases by HED's Hazard Identification Assessment Review Committee (Dobozy, V., 9/28/2001, TXR 0014691) as well as the Metabolism Assessment Review Committee (MARC) (Dobozy, V., 8/14/2001, D274326), both in 2001, it was concluded that S-metolachlor is of comparable or decreased toxicity in comparison to the racemic mixture, metolachlor, and that studies with both chemicals can be used interchangeably for toxicology endpoint selection. The combined metolachlor and S-metolachlor toxicity data bases are adequate to characterize the toxicity of S-metolachlor and metolachlor for risk assessment purposes.

The Hazard and Science Policy Council (HASPOC), based on a weight of evidence (WOE) approach, recommended that a neurotoxicity battery is not required for metolachlor (Van Alstine, J., 03/20/2013, TXR 0056586). The HASPOC also recommended that a subchronic inhalation study with metolachlor is required. Subsequently, this study has been submitted, reviewed and found to be acceptable. The 10X data base uncertainty factor, which was previously applied only for assessing risk for inhalation scenarios, was removed.

The following studies are available for metolachlor:

- Acute Toxicity Battery
- 90-Day Oral Toxicity in the Rat
- Subchronic (6-month) Oral Toxicity in the Dog

- 21-Day Dermal Toxicity in the Rabbit
- Prenatal Developmental Toxicity in the Rat
- Prenatal Developmental Toxicity in the Rabbit
- Reproduction and Fertility Effects in the Rat
- Chronic Toxicity in the Dog
- Chronic Toxicity/Carcinogenicity in the Rat
- Carcinogenicity in the Mouse
- Genetic Toxicology Battery
- Metabolism and Pharmacokinetics in the Rat
- Subchronic (28-day) Inhalation Toxicity in Rats
- Dermal Absorption Study - Rat

The following studies are available for S-metolachlor:

- Acute Toxicity Battery
- 90-Day Oral Toxicity in the Rat
- 90-Day Oral Toxicity in the Dog
- Prenatal Developmental Toxicity in the Rat
- Prenatal Developmental Toxicity in the Rabbit
- Genetic Toxicology Battery
- Metabolism and Pharmacokinetics in the Rat
- Immunotoxicity in Mice

In addition, mechanistic studies were submitted in support of the cancer mode of action and are listed in Appendix A. Studies for metabolites, CGA354743 and CTA51202, are also listed in Appendix A, although they are not used for endpoint selection.

As part of Registration Review for metolachlor and S-metolachlor a broad survey of the literature was conducted to identify studies that report toxicity following exposure to metolachlor via exposure routes relevant to human health pesticide risk assessment not accounted for in the Agency's metolachlor toxicology databases. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 94 studies from the literature. During title/abstract and/or full text screening of this study, one study was identified as containing potentially relevant information (either quantitative or qualitative) for the human health risk assessment. Following a full text review of the identified relevant studies, it was determined that this study does not contain information that would impact the risk assessment and was not considered in the selection of PODs.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Metolachlor is absorbed and metabolized following oral administration in the rat. After oral administration of metolachlor, between 70% and 93% of the administered dose was absorbed. Residual radioactivity at 7 days post-dosing were found in carcass (0.9 - 2.2% of the

administered dose) and red blood cells (0.95 - 1.53 µg equivalents/gram in blood cells for all low dose male and female rats). There was no apparent bioaccumulation of residual radioactivity. Excretion data showed that urine (31-48%) and feces (46-67%) were both significant routes for elimination of metolachlor derived radioactivity. In the low dose groups, the urine appeared more of a predominant route for excretion in female rats (48.5%) than in males (31%), whereas fecal excretion was slightly higher in males (62%) than females (46%). However, at the high oral dose, there were no apparent sex related differences in the pattern of urinary excretion. Metabolism of metolachlor was complex, with up to 32 metabolites identified in urine and/or feces. The major metabolic pathway proposed from analysis of urinary as well as fecal metabolites is one of cleavage of the ether bond and subsequent oxidation to the carboxylic acid, as well as hydrolytic removal of the chlorine atom. Conjugation of metolachlor or metabolites with glucuronic acid or sulfate does not appear to occur.

S-metolachlor is extensively absorbed and metabolized following oral administration. Elimination is via the urine and feces. Tissue residues were highest in whole blood. Irrespective of the dose level, sex of the animal, or repeated exposure, all groups excreted more residue in the feces than in the urine; however, the relative preference for the fecal (over the urinary) route was more pronounced among the male groups. The degree of absorption, based on adding the cumulative urinary excretion to the total residues in tissues, was 35 - 39% in males and 43 - 49% in females. Irrespective of the dose and sex, there seems to be a biphasic plasma profile with two concentration maxima (C_{max}); a fast rising first C_{max} was reached at 0.25 – 1 hour post dosing which was succeeded by a second C_{max} at 8 and at 12 - 24 hours following administration of the low and high dose, respectively. The route or extent of excretion was slightly influenced by the sex of the animal but not by pretreatment with non-radiolabeled S-metolachlor or by the dose level. However, based on the bile duct cannulation study, most of S-metolachlor was absorbed from the gastrointestinal tract since 85% of the dose was recovered in urine, bile fluid, and tissues during the 48 hours study period. Therefore, the biliary excretion and enterohepatic circulation play a significant role in the elimination process of -S-metolachlor.

4.2.1 Dermal Absorption

A dermal absorption study in rats is available for metolachlor (MRID 41833102). An estimated dermal absorption factor (DAF) of 58% was determined based on combined values at 10-hour measurements (33%) and the amount remaining on the skin (25%). The DAF of 58% is conservative because the animals were exposed to the test chemical for a full 24 hours, and the full amount remaining in the skin was included into the dermal absorption value because tape stripping was not conducted.

4.3 Toxicological Effects

In subchronic (metolachlor and S-metolachlor) and chronic (metolachlor) toxicity studies in dogs, rats and mice, decreased body weight was the most commonly observed treatment-related effect. Chronic exposure to metolachlor in rats also resulted in increased liver weight and microscopic liver lesions (foci of cellular alteration) in both sexes. There was no evidence of systemic toxicity at the limit dose in a 21-day dermal toxicity metolachlor study in rabbits, however, dermal irritation was observed at lower doses. There was no evidence of systemic

toxicity at the limit dose in a 28-day inhalation study in rats with metolachlor, although portal of entry effects occurred in the nasal cavity at lower doses. These effects included hyperplasia of the squamous epithelium and subacute inflammation and mucous cell hyperplasia. There was no evidence of immunotoxicity in mice with S-metolachlor.

There was no evidence of a mutagenic or cytogenetic effect *in vivo* or *in vitro* in studies with either metolachlor or S-metolachlor. For metolachlor, there was no evidence of carcinogenicity in mice or male rats; however, there were treatment-related liver tumors in female rats in the chronic toxicity/carcinogenicity study. A mitogenic mode of action was accepted for these tumors. See Section 4.5.3 for further details.

There was no evidence of increased quantitative or qualitative fetal susceptibility in the prenatal developmental studies in rats and rabbits with either metolachlor or S-metolachlor. In general, no developmental toxicity was seen in rats or rabbits with metolachlor and S-metolachlor. In the rat developmental toxicity study with metolachlor, death and clinical signs (clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur) were observed at the limit dose in maternal animals in the absence of developmental effects. In the S-metolachlor rabbit developmental toxicity study, clinical signs of toxicity (little/none/soft stool) were observed in maternal animals in the absence of developmental effects. In the two-generation reproduction study in rats conducted with metolachlor, there was quantitative evidence of susceptibility. Decreased pup body weight in F1 and F2 litters was seen in the absence of maternal toxicity.

The acute toxicity battery of studies for metolachlor showed that it exhibits low acute toxicity via the oral (Toxicity Category III), dermal (Toxicity Category IV), and inhalation (Toxicity Category IV) routes of exposure. It is minimally irritating to the eyes (Toxicity Category III) and skin (Toxicity Category IV) and is a dermal sensitizer.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[2]

The FQPA Safety Factor (SF) is 1X. The toxicity database for S-metolachlor/metolachlor is sufficient for a full hazard evaluation and is considered adequate to evaluate risks to infants and children. Acceptable developmental toxicity studies in the rat and rabbit with both metolachlor and S-metolachlor and an acceptable reproduction study in the rat with metolachlor are available with clearly defined LOAELs and NOAELs. No susceptibility was seen in any of the developmental toxicity studies with rats or rabbits with metolachlor or S-metolachlor. The two--generation reproduction study with metolachlor showed quantitative susceptibility. Decreased pup body weight in F1 and F2 litters was seen in the absence of maternal toxicity. Since this study was used for endpoint selection, the PODs are protective of this quantitative susceptibility. Based on the results of the available toxicity studies, there is no evidence for neurotoxicity.

4.4.1 Completeness of the Toxicology Database

The existing toxicological database for metolachlor and S-metolachlor is adequate for FQPA evaluation. Developmental toxicity studies in rats and rabbits for metolachlor and S-metolachlor

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

and a two-generation reproduction study in rats for metolachlor are available for FQPA consideration. The Hazard and Science Policy Council (HASPOC), based on a WOE approach considering all available hazard and exposure information, recommended that the requirement for acute, subchronic, and developmental neurotoxicity studies be waived (Van Alstine, J., 03/20/2013, TXR 0056586). However, the HASPOC recommended that a subchronic inhalation study with metolachlor was required and that a 10X data base uncertainty factor (UF_{DB}) would be applied only for assessing risk for inhalation exposure scenarios for risk assessment. Subsequently, this study has been submitted, reviewed and found to be acceptable. The 10X database uncertainty factor, which was applied only for assessing risk for inhalation scenarios, was removed.

4.4.2 Evidence of Neurotoxicity

There are no acute or subchronic neurotoxicity studies available for S-metolachlor or metolachlor. In the developmental rat study, clinical signs of neurotoxicity, including clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation were observed in pregnant dams but only at the limit dose of 1000 mg/kg/day. There was no evidence of clinical signs associated with neurotoxicity in adult animals in available subchronic or chronic toxicity studies. The HASPOC, based on a WOE approach, recommended that a neurotoxicity battery is not required for metolachlor (Van Alstine, J., 03/20/2013, TXR 0056586). The PODs selected are protective of the effects seen at this high dose.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Acceptable developmental toxicity studies in the rat and rabbit with both metolachlor and S-metolachlor and an acceptable reproduction study in the rat with metolachlor are available with clearly defined LOAELs and NOAELs. No developmental toxicity was seen in rats or rabbits with either compound. In the metolachlor and S-metolachlor rat prenatal developmental toxicity studies there were developmental effects seen up to the limit dose. In the rat developmental toxicity study with metolachlor, death and clinical signs (clonic and/or tonic convulsions, excessive salivation and lacrimation, urine-stained abdominal fur) were observed at the limit dose in maternal animals in the absence of developmental toxicity. In the S-metolachlor rabbit developmental toxicity study, clinical signs of toxicity (little/none/soft stool) were observed in maternal animals in the absence of developmental effects. In the two-generation reproduction study in rats conducted with metolachlor, there was quantitative evidence of susceptibility. Decreased pup body weight in F1 and F2 litters was seen in the absence of maternal toxicity. The two-generation reproduction study was used for endpoint selection, therefore, the PODs selected are protective of the effects seen at this dose.

4.4.4 Residual Uncertainty in the Exposure Database

There is no residual uncertainty in the exposure database. A conservative chronic dietary exposure analysis was conducted, incorporating tolerance-level residues, HED's 2018 default processing factors, 100% crop treated, and the highest modeled estimated drinking water concentrations. The residential exposure assessment is based on the Residential SOPs and

incorporates chemical specific TTR data. These assessments are not likely to underestimate risks from exposures to metolachlor or S-metolachlor.

4.5 Toxicity Endpoint and Point of Departure Selections

The detailed description of the toxicity studies used for selecting toxicity endpoints and PODs for various exposure scenarios are presented in Appendix A. The specific toxicity endpoints and PODs are presented in Tables 4.5.4.1 and 4.5.4.2. Toxicological endpoints were selected for dietary (food + water), occupational and residential exposure scenarios.

Acute Dietary (General Population): An acute dietary assessment for all populations is not required. The adverse maternal effects resulting from a single dose in the developmental rat study with metolachlor (MRID 00151941) occurred at the limit dose of 1000 mg/kg/day, which is a dose that is not relevant for risk assessment. In addition, an endpoint was not selected for Females 13-49 years old since no developmental effects attributable to a single exposure were identified in the metolachlor/S-metolachlor database.

Chronic Dietary (General Population): The two-generation reproduction study in rats with metolachlor (MRID 00080897) was selected for the chronic dietary endpoint for the general population. The POD is the offspring NOAEL of 26 mg/kg/day. The offspring LOAEL is 86 mg/kg/day based on decreased pup body weight in F1 and F2 litters on lactation days (LDs) 4, 7, 14, and 21. This study is appropriate for the route of exposure (oral) and the population of concern. It is protective of the quantitative susceptibility seen in this study (i.e., decreased pup body weight occurred in the absence of maternal toxicity). The POD selected is protective of the effects seen at this dose as well as of the effects seen in the chronic toxicity/carcinogenicity study. It is appropriate for this duration of concern and is protective of all populations. An UF of 100 was applied to account for interspecies extrapolation (10X), intraspecies variability (10X) and the FQPA Safety Factor of 1X. The cPAD is equivalent to the POD divided by the applicable uncertainty factors, including the FQPA safety factor (cPAD = 0.26 mg/kg/day). The cPAD is protective of chronic toxicity, including carcinogenicity, that could result from exposure to metolachlor/S-metolachlor.

Incidental Oral Children (Short-Term): The two-generation reproduction study in rats with metolachlor (MRID 00080897) was selected for the incidental oral endpoint. The POD is the offspring NOAEL of 26 mg/kg/day. The offspring LOAEL is 86 mg/kg/day based on decreased pup body weight in F1 and F2 litters on lactation days (LDs) 4, 7, 14, and 21. This study is appropriate for the route of exposure (oral) and the population of concern (children 1 to < 2 years old). The POD is protective of the quantitative susceptibility seen in this study (i.e., decreased pup body weight occurred in the absence of maternal toxicity). An uncertainty factor of 100X was applied to endpoints selected for the oral exposure route (10X for interspecies extrapolation, 10X for intraspecies variation, and 1X FQPA SF). The residential level of concern for the margin of exposure (MOE) is 100.

Dermal - Children Only (Short-Term): A route-specific 21-day dermal toxicity study in rabbits with metolachlor (MRID 41833101) is available and produced no adverse systemic effects up to the limit dose of 1000 mg/kg/day. However, quantitative susceptibility has been

identified in the rat 2-generation reproduction study (i.e., decreased pup body weight occurred in the absence of maternal toxicity). Since the 28-day dermal study is not designed to evaluate offspring toxicity by the dermal route it was not selected for risk assessment. Therefore, the 2-generation reproduction toxicity study in the rat (MRID 00080897) was selected for the dermal endpoint to be protective of this susceptibility. The offspring LOAEL of 86 mg/kg/day is based on decreased pup body weight in F1 and F2 litters. The POD is the offspring NOAEL of 26 mg/kg/day. The total Uncertainty Factor is 100X (10X for inter-species, 10X for intra-species extrapolation, and 1X FQPA SF). As discussed in Section 4.1.2, the dermal absorption factor for this risk assessment is 58%. The offspring NOAEL/LOAEL in this study is an oral dose of 26/86 mg/kg/day, respectively, with an estimated dermal absorption factor of 58%. Using this dermal absorption factor, the dermal equivalent NOAEL/LOAEL would be 45/148 mg/kg/day which is below the dermal limit dose of 1000 mg/kg/day for assessing dermal risk. It is appropriate for the exposure duration and population of concern (children).

Dermal - Adults (Short- and Intermediate-Term): A dermal assessment is not required since no systemic effects were seen up to the limit dose of 1000 mg/kg/day in a 21-day dermal toxicity study in rabbits with metolachlor. In addition, the quantitative susceptibility seen in the offspring in the two-generation reproduction study is not relevant for adults.

Inhalation (All Populations) (Short- and Intermediate-Term): A route-specific 28-day inhalation toxicity study in rats (MRID 50410101) was used for the short- and intermediate-term inhalation endpoint. The portal of entry NOAEC is 0.1 mg/L (equivalent to 100 mg/m^3). The portal of entry LOAEC is 0.3 mg/L (300 mg/m^3) based on hyperplasia of the squamous epithelium and subacute inflammation in both sexes, and mucous cell hyperplasia in males at nasal level II. This route specific study is appropriate for the duration and population of concern. It provides a lower POD (Human Equivalent Doses) than the two-generation reproduction study and is, therefore, protective of quantitative susceptibility seen in that study. See human equivalent doses in Table 4.5.4.3. The occupational inhalation level of concern is 30X (3x for interspecies extrapolation, 10x for intraspecies variation). The database uncertainty factor of 10X that was previously required for the lack of an inhalation toxicity study in no longer relevant.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

For children, oral and dermal exposures can be combined since the incidental oral and dermal PODs are based on the same study (two-generation reproduction study) and endpoint (decreased body weights). For adults, dermal and inhalation routes cannot be combined since there is no dermal endpoint.

4.5.2 Cancer Classification and Risk Assessment Recommendation

For metolachlor, there was no evidence of carcinogenicity in male or female mice or male rats; however, there were treatment-related liver tumors in female rats. There was no evidence of a mutagenic or cytogenetic effect *in vivo* or *in vitro* in studies with either metolachlor or S-metolachlor. In 1994, metolachlor was classified as a Group C, possible human carcinogen, based on liver tumors in rats at the highest dose tested according to the 1986 Guidelines for Carcinogen Risk Assessment (Dapson, S. and Rinde, E., 11/16/1994, TXR 0011347).

Quantification of risk using a non-linear approach (i.e., reference dose (RfD)) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to metolachlor. However, in 2017, EPA re-assessed the cancer classification for metolachlor based on mechanistic studies submitted to support a human relevance framework analysis for a mitogenic mode of action (MOA) for liver tumors in female rats. The CARC concluded that the *in vitro* and *in vivo* data adequately demonstrated dose and temporal concordance to support key events for the MOA leading to liver tumors in female rats. In the absence of a long-term carcinogenicity study with S-metolachlor, the tumorigenic effects of metolachlor can be reasonably explained by constitutive androstane receptor (CAR) activity demonstrated in the MOA for S-metolachlor. This is supported by the comparable effects of S-metolachlor and metolachlor on CYP2B expression/BROD activity and liver hypertrophy. Consequently, in accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March 2005), the Cancer Assessment Review Committee (CARC) concluded that metolachlor/S-metolachlor should be reclassified as "Not Likely to be Carcinogenic to Humans" at doses that do not induce cellular proliferation in the liver. This classification was based on convincing evidence that a mitogenic mode of action for liver tumors in female rats has been established and that the carcinogenic effects have been demonstrated as a result of a MOA dependent on CAR activation. Based on this cancer classification, the quantification of cancer risk using a Q_1* approach is not required. A non-linear approach (i.e., RfD) would adequately account for all the chronic toxicity, including carcinogenicity, that could result from exposure to metolachlor/S-metolachlor. The RfD should be protective of the dose which induced hepatocellular proliferation (150 mg/kg/day or 3000 ppm) in the female rat. (Dobreniecki, S., 11/06/2017, TXR 0057654).

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

The points of departure, uncertainty factors, and toxicity endpoints are presented in the following tables.

Table 4.5.3.1 Summary of Toxicological Doses and Endpoints for Metolachlor/S-metolachlor for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary *(All Populations)*	An acute dietary assessment for all populations is not required. The adverse effects resulting from a single dose in the developmental rat study with metolachlor occurred at the limit dose of 1000 mg/kg/day, which is a dose that is not relevant for risk assessment. In addition, an endpoint was not selected for Females 13-49 years old since no developmental effects attributable to a single exposure were identified in the metolachlor/S-metolachlor database.			
Chronic Dietary *(All Populations)*	NOAEL= 26 mg/kg/day	UF_A= 10X UF_H=10X FQPA SF= 1X	cRfD=cPAD = 0.26 mg/kg/day	Two-Generation Reproduction Study in Rats (Metolachlor) (MRID 00080897) Offspring LOAEL = 86 mg/kg/day based on decreased pup body weight in F1 and F2 litters

Table 4.5.3.1 Summary of Toxicological Doses and Endpoints for Metolachlor/S-metolachlor for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral Short-term (1-30 days)	NOAEL= 26 mg/kg/day	UF_A= 10X UF_H=10X FQPA SF= 1X	LOC for MOE = 100	Two-Generation Reproduction Study in Rats (Metolachlor) (MRID 00080897). Offspring LOAEL = 86 mg/kg/day based on decreased pup body weight in F1 and F2 litters
Dermal Short- and Intermediate-Term (1-6 months) *(Children only*)*	NOAEL= 26 mg/kg/day DAF = 58%	UF_A= 10X UF_H=10X FQPA SF= 1X	LOC for MOE = 100	Two-Generation Reproduction Study in Rats (Metolachlor) (MRID 00080897). Offspring LOAEL = 86 mg/kg/day based on decreased pup body weight in F1 and F2 litters
Dermal Short- and Intermediate-Term (1-6 months) *(Adults only)*	A dermal assessment is not required since no systemic effects were seen up to the limit dose of 1000 mg/kg/day in a 21-day dermal toxicity study in rabbits with metolachlor. In addition, the quantitative susceptibility seen in the offspring in the 2-generation reproduction study is not relevant for adults.			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months) *(All populations)*	Portal of Entry NOAEC= 0.1 mg/L (equivalent to 100 mg/m^3) See Table 4.5.4.3 for HEC/HED calculations	UF_A= 3X UF_H=10X FQPA SF=1X	LOC for MOE = 30	28-day Inhalation Toxicity Study Rat – Metolachlor (MRID 50410101) Portal of Entry LOAEC is 0.3 mg/L (300 mg/m^3) based on hyperplasia of the squamous epithelium and subacute inflammation in both sexes, and mucous cell hyperplasia in males at nasal level II.
Cancer (oral, dermal, inhalation)	Classification: Metolachlor/S-metolachlor has been classified as "Not Likely to be Carcinogenic to Humans" at doses that do not induce cellular proliferation in the liver, with risk quantitated using a non-linear (RfD) approach. Dobreniecki, S., 06-NOV-2017, TXR 0057654			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. NOAEC = no observed adverse effect concentration. LOAEL = lowest observed adverse effect level. LOAEC = lowest observed adverse effect concentration. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. (a = acute, c = chronic). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. *Children only POD is relevant for all non-adult non-occupational/residential exposure scenarios.

Table 4.5.3.2 Summary of Toxicological Doses and Endpoints for Metolachlor/S-metolachlor for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1-6 months)	A dermal assessment is not required since no systemic effects were seen up to the limit dose of 1000 mg/kg/day in a 21-day dermal toxicity study in rabbits with metolachlor. In addition, the quantitative susceptibility seen in the offspring in the 2-generation reproduction study is not relevant for adults.			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	Portal of Entry NOAEC= 0.1 mg/L (equivalent to 100 mg/m^3) See Table 4.5.4.3 for HEC/HED calculations	UF_A= 3X UF_H=10X	LOC for MOE = 30	28-day Inhalation Toxicity Study Rat – Metolachlor (MRID 50410101) Portal of Entry LOAEC is 0.3 mg/L (300 mg/m^3) based on hyperplasia of the squamous epithelium and subacute inflammation in both sexes, and mucous cell hyperplasia in males at nasal level II.
Cancer (oral, dermal, inhalation)	Classification: Metolachlor/S-metolachlor has been classified as "Not Likely to be Carcinogenic to Humans" at doses that do not induce cellular proliferation in the liver, with risk quantitated using a non-linear (RfD) approach. Dobreniecki, S., 06-NOV-2017, TXR 0057654			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. NOAEC = no observed adverse effect concentration. LOAEL = lowest observed adverse effect level. LOAEC = lowest observed adverse effect concentration. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.5.3.3. Summary of Human Equivalent Concentration (HEC)/Human Equivalent Dose (HED) values for Metolachlor*.

Population	Scenario	Toxicity Duration Adjustment[a]		HEC[b]		HED (mg/kg/day)[c]
		Daily (hrs/day)	Weekly (days/wk)	mg/L	mg/m^3	
Occupational	Handler	8	5	0.018	17.625	1.668
Residential	Handler	NA	NA	0.024	23.500	0.556
	Outdoor post-application	NA	NA	0.024	23.500	0.639
	Indoor post-application	NA	7	0.017	16.786	0.397
	Bystander	24	7	0.004	4.196	NA

*The inhalation values have been calculated based on the 2016 revised spreadsheets. The HED calculation has been revised to be based on the same breathing rate used to derive the HEC – resulting in a single HED as the toxicological point of departure. In 6terms of risk estimates, the effect of this error correction is not unidirectional – some previously-calculated risks will be higher, while some will be lower.

NA = not applicable (the expected duration of the exposure scenario is less than the duration in the available inhalation toxicity studies; downward adjustments are not permitted).

[a] Toxicity duration adjustment from 6 hours/day, 5 days/week for 4 weeks (20-21 exposures) in the route-specific inhalation study.

[b] HEC =human-equivalent concentration; HEC = rat POD x daily duration adjustment x weekly daily duration adjustment x RDDR. ***RDDR (extrathoracic) =0.235; MMAD=2.60; Sigma g = 2.34; Body weight = 299 g (avg of male and female from study);***

[c] HED =human-equivalent dose; HED = HEC (mg/L) x human specific conversion factor (11.8 L/hr-kg) x respiratory tract to oral absorption ratio (1) x duration of daily exposure for activity (occupational handler = 8 hrs/day, residential handler and indoor post-application = 2 hrs/day, residential outdoor post-application = 2.3 hrs/day).

4.6 Endocrine Disruptor Screening Program

As required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of the reregistration decision for metolachlor and S-metolachlor, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), metolachlor and S-metolachlor are subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a

chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[3] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Metolachlor is on List 1 for which EPA has received all of the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see Docket # EPA-HQ-OPP-2014-0772 for metolachlor). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[4]

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The Agency has previously concluded that the residues of concern for metolachlor and S-metolachlor in livestock and plants including rotational crops for both tolerances and risk assessment are metolachlor/S-metolachlor and its metabolites, determined as the derivatives CGA-37913 and CGA-49751, each expressed as the parent compound. Considering the structural similarity to parent metolachlor/S-metolachlor, the Residue of Concern Knowledgebase Subcommittee (ROCKS) recommended the following environmental degradates—CGA-51202 (metolachlor- oxanilic acid (OA)), CGA-40172, and CGA-50720—to be included as residues of concern for drinking water in addition to parent metolachlor/S-metolachlor (Hummel, S., 12/3/2014, D424250).

[3] See https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[4] https://www.epa.gov/endocrine-disruption

Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression			
Matrix		**Residues included in Risk Assessment**	**Residues included in Tolerance Expression**
Plants	Primary Field Crop	Metolachlor/S-metolachlor, and its metabolites convertible to the derivatives CGA-37913 and CGA-49751	Metolachlor/S-metolachlor, and its metabolites convertible to the derivatives CGA-37913 and CGA-49751
	Rotational Crop	Metolachlor/S-metolachlor, and its metabolites convertible to the derivatives CGA-37913 and CGA-49751	Metolachlor/S-metolachlor, and its metabolites convertible to the derivatives CGA-37913 and CGA-49751
Livestock	Ruminant & Poultry	Metolachlor/S-metolachlor, and its metabolites convertible to the derivatives CGA-37913 and CGA-49751	Metolachlor/S-metolachlor, and its metabolites convertible to the derivatives CGA-37913 and CGA-49751
Drinking Water		Metolachlor/S-metolachlor, and its degradates: CGA-51202 (metolachlor-OA), CGA-40172, and CGA-50720	Not Applicable

5.2. Food Residue Profile

The existing residue chemistry database for metolachlor/S-metolachlor is adequate for Registration Review. Adequate plant and livestock metabolism data, magnitude of the residue data (*i.e.*, field trials and processing studies), confined rotational crop data, and storage stability data are available to support the food/feed uses of metolachlor/S-metolachlor and the established tolerances.

Metolachlor and S-metolachlor are applied to a variety of crops as preplant, preplant incorporated, preemergence, or postemergence herbicides to control grass weeds. Residues of metolachlor on crops from early season applications are generally low. Crop residues from field trials conducted with corn, onion bulbs, berries, leafy vegetables, fruiting vegetables, legume vegetables, cucurbit vegetables and root and tuber vegetables are low, ranging from <0.08 ppm (combined LOQs for CGA-37913 and CGA-49751, expressed in parent equivalents, of 0.03 and 0.05 ppm, respectively) to 1.76 ppm with a few exceptions— cilantro fresh leaves (4.1 ppm) and stevia dried leaves (5.88 ppm). Although residues did concentrate slightly in some processed commodities such as tomato paste (2.2x), tomato puree (1.4x) and sugar beet molasses (5x), residues in processed commodities from field trials conducted at exaggerated use rates (e.g. 5x) were also low, ranging from 0.27 ppm (tomato paste) to 1.65 ppm (sugar beet molasses).

Sufficient rotational crop studies were conducted to support the following plant-back intervals (PBIs) for rotational crops: 2 months for small grains (barley, oats, rye and wheat) that can be planted in the fall, 7 months for small grains that can be planted in the following spring, and 60 days for vegetable crops.

Secondary transfer of residues may occur indirectly in milk and edible tissues of livestock animals as a result of ingestion of feedstuffs such as: field corn grain, forage, and stover; peanut hay, peanut meal, soybean hay and forage, etc. Based on the ruminant feeding study, maximum combined residues of metolachlor, and its metabolites convertible to the derivatives CGA-37913 and CGA-49751 and expressed in parent equivalents from exposure to metolachlor/S-metolachlor-treated feedstuffs in fat, kidney, liver, meat, and milk were low, estimated at 0.011 ppm, 0.18 ppm, 0.057 ppm, 0.016 ppm and 0.004 ppm, respectively. Based on poultry feeding study, maximum combined residues from exposure to metolachlor/s-metolachlor-treated feedstuffs in egg, fat, meat and meat byproducts were also low, estimated at 0.006 ppm, 0.006 ppm, 0.0108 ppm and 0.0108 ppm, respectively.

The residue studies were supported by adequate storage stability data. These data indicate that the metolachlor or S-metolachlor derivatives CGA-49751 and CGA-37913 are stable during frozen storage for at least 17 months in/on plant commodities. For livestock commodities, data are available indicating that CGA-49751 is stable at -15°C for up to 25 months in milk, eggs, beef liver and muscle. The derivative CGA-37913 is stable at -15°C for up to 25 months in milk and eggs, 12 months in beef liver, and 2 months in beef muscle.

5.3 Water Residue Profile

For the Registration Review of metolachlor and its registered active isomer, S-metolachlor, the Environmental Fate and Effects Division (EFED) updated the estimated drinking water concentrations (EDWCs) with the available new environmental fate data using the Pesticide Water Calculator (PWC) (Antoline, J., 10/31/2018, D448964). The maximum chronic EDWC **decreased** from the previous value of 978 ug/L to 830 ug/L (based on groundwater modeling). Subsequently, EFED incorporated the SLN (Special Local Needs) max use rate which did not result in any changes in the updated EDWCs. Therefore, the maximum chronic EDWC remains 830 ug/L for groundwater (e-mail communication between G. Orrick and A. Jakob, 9/4/2019). With no new uses established or proposed since the most recent risk assessment (Kidwell, J. *et al.*, 9/27/2018, D447125,) and a lower updated EDWC, the risk estimates of food and drinking water for metolachlor/S-metolachlor of the previous 2018 dietary assessment (Keel¸ S., 9/17/2018, D447126) continue to be applicable for Registration Review.

The drinking water residues used in the dietary risk assessment were provided by EFED in 2014 (Koper, C., 12/16/2014, D420047). Using a total toxic residues approach, EFED included residues of concern identified by ROCKS—parent (metolachlor/S-metolachlor), CGA 51202, CGA-40172, and CGA-50720 in the assessment. The highest EDWCs were from a Tier II PRZM-GW (Pesticide Root Zone Model-Ground Water) modeling at a maximum annual application rate of 4 lbs ai/A for registered crops (corn/cotton). The EDWCs for a 30-year average were used in the chronic assessment. The EDWC of metolachlor/S-metolachlor and its degradates in surface water from chronic exposure was minimal (21.80 µg/L). The EDWC of metolachlor/S-metolachlor and its degradates in ground water from chronic exposure, 978 µg/L, was used in the assessment. Water residues of 0.978 ppm were incorporated directly in the DEEM-FCID food categories “water, direct, all sources” and “water, indirect, all sources.”

The sources of EDWCs provided by EFED (Koper, C., 12/16/2014, D420047) and EFED's final estimates are indicated in Table 5.3.1.

Table 5.3. Recommended EDWCs for Metolachlor/ S-Metolachlor Human Health Risk Assessment

Drinking Water Source	Crop Scenario	1-in-10 year acute (µg/L)	1-in-10 year chronic (µg/L)	30- year average cancer chronic (µg/L)
Surface Water	MS Corn [1] (aerial)	371	--	--
	CA Lettuce [2] (aerial)	--	43.70	21.80
Ground Water	NC Cotton [3] (aerial)	1060	NA	--
	WI Corn [3] (aerial)	--	NA	**978**

[1] EDWC calculated from the maximum rate (2 apps x 2.0 lbs a.i./A) registered on corn and cotton generated using SWCC model (aerial application; TTR approach) with a PCA factor of 0.91.
[2] Current proposed use on lettuce (2 apps x 0.95 lbs a.i./A x 2 seasons).
[3] Highest EDWCs generated using PRZM-GW model based on a 30 year simulation of 2 foliar applications of 2.0 lbs a.i./A for a maximum annual rate of 4.0 lbs a.i/A for corn/cotton (Metolachlor RED; D185152, 172022).

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Metolachlor is a racemic mixture that consists of *R*-enantiomer and *S*-enantiomer (50% each). The S-metolachlor product is an isomer-enriched formula comprised of 88% *S*-isomer and 12% *R*-isomer. Adequate information indicates that the metabolism of *S*-metolachlor is essentially the same as for metolachlor. The residues of concern for S-metolachlor are the same as those for metolachlor (Kutney, L., 11/15/1996, D226780).

A conservative chronic dietary exposure analysis was conducted, incorporating tolerance-level residues. Tolerances for residues of metolachlor in or on plant and livestock commodities are currently expressed in terms of the combined residues (free and bound) of metolachlor and its metabolites, determined as the derivatives, CGA-37913 and CGA-49751, each expressed as the parent compound [(40 CFR §180.368 (a)(1), c(1) & d (1)]. Tolerances for residues of S-metolachlor in or on plant and livestock commodities are also expressed in terms of the combined residues (free and bound) of S-metolachlor, its R-enantiomer and its metabolites, determined as the derivatives, CGA-37913 and CGA-49751, calculated as the stoichiometric equivalent of S-metolachlor, in or on the commodity [(40 CFR §180.368 (a)(2), c(2) & d (2)]. In cases where separate tolerance listings occur for both metolachlor and S-metolachlor on the same commodity, the higher value of the two is used in the analyses, or if equal, either one was used. For the drinking water residues please see Section 5.3.

Chronic dietary exposure assessments were conducted using the DEEM-FCID, Version 3.16, which incorporates 2003-2008 consumption data from USDA's NHANES/WWEIA. The data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g., apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by

USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups.

For a chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

5.4.2. Percent Crop Treated Used in Dietary Assessment

The chronic dietary exposure analysis assumed 100% crop treated.

5.4.3 Acute Dietary Risk Assessment

An acute dietary endpoint (i.e., single dose endpoint) for risk assessment was not identified in the toxicity database for the general U.S. population or any other subpopulation; therefore, an acute dietary assessment was not conducted.

5.4.4 Chronic Dietary Risk Assessment

A conservative chronic dietary exposure analysis was performed for the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50-99 years old. The resulting dietary (food and water) chronic exposure estimates are not of concern (<100% cPAD) for the general U.S. population (8.7% cPAD) and all population subgroups; the most highly exposed population subgroup was all infants <1 year old with 22% of the cPAD.

Residues in drinking water were the major risk contributor. Results from the "food only" assessments indicate that the most highly-exposed population subgroup in chronic analyses was children 1-2 years old with a risk estimate (food only) at 2.1% of the cPAD. This value is significantly lower than the highest exposure and risk estimates from the "food + water" assessments, 22% cPAD for the population subgroup of all infants <1 year old.

5.4.5 Cancer Dietary Risk Assessment

Metolachlor/S-metolachlor has been classified as "Not Likely to be Carcinogenic to Humans" at doses that do not induce cellular proliferation in the liver. A non-linear approach (i.e., RfD) would adequately account for all chronic toxicity, including carcinogenicity. The chronic RfD is protective of the dose which induced hepatocellular proliferation in the female rat.

5.4.6 Summary Table

Table 5.4.6.1 Summary of Dietary Food and Drinking Water Exposure and Risk for S-metolachlor and Metolachlor.		
Population Subgroup	**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% cPAD***
General U.S. Population	0.022657	8.7
All Infants (<1 year old)*	**0.056203**	**22**
Children 1-2 years old	0.034950	13
Children 3-5 years old	0.029489	11
Children 6-12 years old	0.020980	8.1
Youth 13-19 years old	0.016750	6.4
Adults 20-49 years old	0.022277	8.6
Adults 50-99 years old	0.022005	8.5
Females 13-49 years old	0.022208	8.5

*The subpopulation with the highest risk estimates is bolded.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Metolachlor
There are currently no metolachlor products registered for homeowner use and no products registered for application to residential areas.

S-Metolachlor
There are currently no S-metolachlor products registered for homeowner use, however, there are registered uses for application to residential areas. The existing residential uses were previously assessed to reflect updates to the toxicological endpoints and HED's 2012 Residential SOPs[5] along with policy changes for body weight assumptions (Van Deusen, B., 9/25/2018, D447124). The residential post-application risk estimates did not exceed HED's level of concern (MOEs ≥100) using chemical specific TTR data. Since dislodgeable foliar residue (DFR) data were not available, default exposure data were used for assessment of post-application exposures to treated gardens and incorporated a time-weighted average residue rather than a repeated daily "day 0" residue point estimate that does not account for dissipation. Additional data on dislodgeable foliar residues are not recommended as the data is not expected to further EPA's general understanding of the availability of pesticide residues on foliar surfaces for residential landscape plantings or ornamental gardens.

6.1 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.1.1 reflects the residential risk estimates that were recommended for use in the aggregate risk assessment for S-metolachlor in 2018 (Van Deusen, B., 9/25/2018, D447124).

[5] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

- The recommended residential exposure for use in the youth 11 to <16 years old aggregate assessment is dermal exposures from post-application exposure to treated turf during golfing activities.
- The recommended residential exposure for use in the children 6 to <11 years old aggregate assessment is dermal exposures from post-application contact with treated gardens.
- The recommended residential exposure for use in the children 1 to <2 years old aggregate assessment is dermal and hand-to-mouth exposures from post-application exposure to treated turf.

Table 6.1.1. Recommendations for the Residential Exposures for the S-Metolachlor Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Youths (11 to <16 years)	Post-application exposure to treated turf during golfing activities	0.0041	NA	NA	0.0041	6,300	NA	NA	6,300
Child (6 to <11 years)	Post-application exposure from contact with treated gardens	0.22	NA	NA	0.22	120	NA	NA	120
Child (1 to <2 years)	Post-application exposure to treated turf	0.089	NA	0.0013	0.090	290	NA	20,000	290

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed.
2 MOE = the MOEs associated with the highest residential exposures.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Food and residential exposures from S-metolachlor have been aggregated since those exposure pathways are relevant for risk assessment.

7.1 Acute Aggregate Risk

An acute dietary endpoint (i.e., single dose endpoint) for risk assessment was not identified in the toxicity database for the general U.S. population or any other subpopulation; hence, an acute aggregate assessment was not conducted.

7.2 Short-Term Aggregate Risk

Short-term aggregate assessments include exposures that will occur from one to thirty days. There is potential for residential exposure to S-metolachlor from use of registered products which are applied to residential turf or gardens. The potential short-term residential risk scenarios recommended for aggregate assessment are: 1) post-application exposure to treated turf during golfing activities (youth 11 to <16 years old); 2) post-application contact with treated gardens (children 6-11 years old); and 3) post application exposure from dermal and hand-to-

mouth contact with treated turf (children 1 to <2 years old). Refer to Section 6.1 for the residential exposures that are likely to be combined. Results from that assessment have been used to assess aggregate risk from exposure to food, drinking water, and residential lawns for this analysis. Based on this analysis, short-term aggregate MOEs are not of concern.

Table 7.2.1. Short-Term Aggregate Risk Calculations.

Population	Short- Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Youths (11 to <16 years)	26	100	0.26	0.016750	0.00411	0.02086	1,200
Child (6 to <11 years)	26	100	0.26	0.020980	0.224	0.24498	110
Child (1 to <2 years)	26	100	0.26	0.034950	0.0904	0.12535	210

[1] Youth and child LOC = 100 (10X for interspecies extrapolation, 10X for intraspecies variation, 1X for FQPA SF).
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Residential Exposure = [Oral exposure + Dermal exposure]. Source of residential exposure values used in aggregate assessment (Table 6.2.2).
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure.
[5] Aggregate MOE = [NOAEL 26 mg/kg/day ÷ (Avg Food & Water Exposure + Residential Exposure)].

7.3 Intermediate-Term Aggregate Risk

Intermediate-term aggregate assessments include exposures that will occur from thirty days to six months. There are no residential scenarios which are expected to be intermediate-term.

7.4 Chronic Aggregate Risk

Chronic or long-term aggregate assessments include exposures that will exceed six months. The chronic risk estimates include exposure to residues of S-metolachlor in food and drinking water, and do not include dermal, inhalation or incidental oral exposures. Since the dietary exposure assessment already includes the highest chronic exposures from the drinking water modeling data, no further calculations are necessary. The chronic risk estimates for all populations, resulting from aggregate exposure to S-metolachlor in food and drinking water are below EPA's level of concern. The food and drinking water exposure estimate for the most highly exposed subgroup is 22% of the cPAD for all infants <1 year old. See Section 5.4.4 for a detailed discussion of the chronic dietary assessment.

7.5 Cancer Aggregate Risk

As the risks estimated based on the chronic reference dose are protective of cancer effects, no separate cancer risk assessment is necessary. The chronic dietary aggregate risk assessment is below the Agency's level of concern.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[6] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

Two S-metolachlor products have existing labels for use on turf, thus it was considered whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. If the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. Note that this assumes similar formulations are being applied to the agricultural crops and the residential turf (i.e., if a granular product is registered for use on residential turf, the scenarios assessed for that use may not be protective of liquid applications made to agricultural crops). The currently registered maximum single application rate of S-metolachlor for alfalfa is 3.17 lb ai/A. The highest degree of spray drift noted for any application method immediately adjacent to a treated field (Tier 1 output from the aerial application using fine to medium spray quality) results in a deposition fraction of 0.26 of the application rate. A quantitative spray drift assessment for metolachlor and S-metolachlor is not required because the maximum application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate [(2.48 lb ai/A)][7] for any S-metolachlor product. The turf post-application risks have been previously assessed and are not of concern (see Section 6 of this document).

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues

[6] This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.
[7] 3.17 lb ai/A x 0.26 ≤ 2.48 lb ai/A

related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009 and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for metolachlor/S-metolachlor.

In addition to this screen, the Agency has developed a preliminary bystander volatilization inhalation exposure assessment for metolachlor/S-metolachlor utilizing the currently available inhalation toxicity and air monitoring data.

Air monitoring data is available for metolachlor/S-metolachlor through California's Department of Pesticide Regulation (DPR) Air Monitoring Network (AMN) and Air Resources Board (ARB). Two monitoring studies (Pesticide Air Monitoring in Parlier, CA, 2009, & Ambient Air Monitoring for Pesticides in Lompoc, CA, 2003) were conducted for metolachlor/s-metolachlor as part of the ARB program to conduct air monitoring studies for pesticides that are candidate toxic air contaminants. Metolachlor/S-Metolachlor have also been monitored as part of the AMN's ambient air sampling for multiple pesticides in multiple communities from 2011 through 2017 (Volumes 1 – 7). All results from the available post-application or ambient air monitoring data for metolachlor/S-metolachlor were less than the limit of quantification (LOQ); therefore, a quantitative assessment has not been conducted.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to metolachlor/S-metolachlor and any other substances and metolachlor/S-metolachlor does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that metolachlor/S-metolachlor has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[8] and conducting cumulative risk assessments (CRA)[9]. During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for metolachlor/S-metolachlor suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level

[8] Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)
[9] Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)

toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

11.1 Short-/Intermediate-Term Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios identified in Tables F.1 and F.2 of Appendix F.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor are detailed below on an individual basis.

Application Rate:
The maximum single application rates for the registered uses are provided in Tables E.1 and E.2 of Appendix E.

Unit Exposures:
It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the ORETF database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[10]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[11].

For the dry bulk fertilizer scenarios, HED assumed a closed mixing/loading scenario for commercial impregnation of dry bulk fertilizer, and an open mixing/loading scenario for grower-owned equipment impregnation of dry bulk fertilizer. For all applications of dry bulk fertilizer, HED assumed the use of an open-cab spreader.

[10] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[11] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Area Treated or Amount Handled:
The inputs for area treated or amount handled were based on information in ExpoSAC Policy 9.1.

HED does not have data regarding the mixing/loading or the application of metolachlor/S-metolachlor-impregnated dry bulk fertilizer. The mixing/loading processing rate for commercial impregnation of dry bulk fertilizer has been estimated to be 960 tons of fertilizer processed per 8 hour day based on information supplied by a registrant concerning the chemical alachlor (as referenced in its reregistration eligibility document (RED) document[12]). Mixing/loading for on-farm impregnation of dry bulk fertilizer was then assessed using an estimate of 160 acres/day. Application of dry bulk fertilizer was assessed assuming application to up to 320 acres/day for commercial equipment and 160 acres/day for grower-owned equipment.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). For metolachlor/S-metolachlor, based on the proposed uses and label directions, short- and intermediate-term exposures are expected. Since the same endpoint and POD was selected for short- and intermediate-term durations, short-term exposure and risk estimates are considered to be protective of potential intermediate-term exposure and risk.

Personal Protective Equipment: Estimates of inhalation exposure were calculated for various levels of PPE. Results are presented for the currently proposed "baseline" level of attire, defined as no respirator. Registered metolachlor labels require applicators and other handlers to wear coveralls over short- or long-sleeved shirt and short- or long pants, chemical resistant gloves, chemical resistant footwear plus socks, chemical resistant headgear for overhead exposure, and chemical resistant apron when cleaning equipment, mixing, or loading. Mixers and loaders supporting aerial applications are required to use closed systems.

All registered S-metolachlor labels require occupational handlers to wear, at a minimum, baseline attire (long sleeved shirt, long pants, shoes, and socks), and waterproof and/or chemical resistant gloves. For certain activities/products, additional PPE is required such as, coveralls and/or protective eyewear.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in the ORE document that supports this risk assessment (Van Deusen, B., 9/6/2019, D452743).

[12] Available: https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-090501_1-Dec-98.pdf

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

For the occupational handler assessment, a screening-level approach was used which combined registered crops into surrogate groups and assessed the maximum application rate per group to assess all potential exposure scenarios. None of the occupational handler scenarios result in short-and intermediate-term inhalation risk estimates of concern (i.e., MOEs are ≥ 30, ranging from 36 to 180,000) at baseline level of attire or engineering controls for metolachlor or S-metolachlor. Tables F.1 and F.2 of Appendix F present the short- and intermediate-term inhalation risk estimates for metolachlor and S-metolachlor, respectively.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure during aerial applications (covering both airplanes and helicopters) of liquid formulations to pilots in enclosed cockpits (data from AHETF) and of granule formulations in enclosed cockpits (data from PHED). Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); use of the data in this fashion is consistent with the Agency's Worker Protection Standard (WPS) stipulations for engineering controls, which says label-required PPE for applicators can be reduced when using an enclosed cockpit (40 CFR 170.240(d)(6)(iii)) as well as a provision regarding use of gloves for aerial applications (40 CFR 170.240(d)(6)(i)), which says pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

11.2 Short-/Intermediate-Term Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.2.1 Dermal Post-Application Exposure and Risk Estimates

Since there is no adult dermal hazard associated with metolachlor/S-metolachlor, a quantitative dermal post-application exposure assessment was not conducted.

Restricted Entry Interval: Metolachlor and S-metolachlor are classified as Toxicity Category III for acute oral exposures. Metolachlor is classified as Toxicity Category IV for acute dermal exposures and S-metolachlor is category III. Metolachlor and S-metolachlor are classified at Toxicity Category IV for inhalation routes. They are classified as category IV for skin irritation potential and category III for eye irritation toxicity. They are both skin sensitizers. Under 40 CFR §156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation, and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement REI on registered labels (12 to 24 hours) are adequate to protect agricultural workers from post-application exposures to metolachlor/S-metolachlor.

11.2.2 Inhalation Post-Application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for metolachlor/S-metolachlor.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

12.0 Incident and Epidemiological Data Review

A Tier 1 update review summary of recent incident data from Incident Data System (IDS) and National Institute of Occupational Safety and Health (NIOSH) Sentinel Event Notification

System for Occupational Risk (SENSOR)-Pesticides as per standard protocol under the Agency's Registration Review Program was conducted (Recore, S *et a*l., 9/12/2019, D452762).

One component of this program is consideration of human incident data. In conjunction with a human health risk assessment based on other data sources, such human incident data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products. In the IDS analysis from January 1, 2014 to June 14, 2019, no metolachlor incidents were reported to either Main or Aggregate IDS. From January 1, 2014 to June 14, 2019, no S-metolachlor incidents involving a single active ingredient and nine S-metolachlor incidents involving multiple active ingredients were reported to Main IDS and were classified as moderate severity; there were 32 S-metolachlor incidents reported to Aggregate IDS. Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). A query of the SENSOR-Pesticides 1998-2015 identified 17 cases involving metolachlor. All 17 cases involved multiple active ingredients, one of which was either metolachlor or s-metolachlor. Sixteen cases were low in severity and one case was moderate in severity. The single moderate severity case was occupational, involving an agricultural handler who was spraying a field with a total of five pesticide products, one of which was S-Metolachlor Technical. The mixture of products leaked onto the handler while he was making the field application. He became disoriented in the field. He also reported: restlessness, muscle weakness, dizziness, drowsiness, abdominal pain/irritation, and nausea.

The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the U.S. National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention's NIOSH, and the United States Environmental Protection Agency (EPA). Metolachlor is included in the AHS, and – overall -- there is insufficient evidence to conclude that a clear associative or causal relationship exists between metolachlor exposure and the carcinogenic and non-carcinogenic health outcomes assessed in the 53 AHS publications reported here. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

Conclusion: Based on the continued low frequency and severity of metolachlor incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time. With respect to epidemiology, there is insufficient evidence at this time to conclude that a clear associative or causal relationship exists between metolachlor exposure and the carcinogenic and non-carcinogenic health outcomes assessed in the AHS studies reported here. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

13.0 References

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Dobreniecki, S. 11/6/2017. TXR 0057654. Metolachlor/S-metolachlor: Report of the Cancer Assessment Review Committee (5th Evaluation).

Hummel, S. 12/3/2014. D424250. Metolachlor and S-Metolachlor**.** Recommended Environmental Degradates to Include in Drinking Water Assessment.

Keel, S. 9/17/2018. D447126. S-metolachlor **-** Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for (1) Establishment of Tolerances for New Uses on Chicory, Stevia and Swiss Chard; (2) Tolerance Translations from Table Beet Tops, Turnip Greens, and Radish Tops to Crop Group 2 (Leaves of Root and Tuber Vegetables), except Sugar Beets; (3) Tolerance Conversions (i) from Crop Subgroup 4B to Crop Subgroup 22B (Leaf Petiole Vegetable), (ii) from Crop Subgroup 5A to Crop Group 5-16 (*Brassica*, Head and Stem Vegetable) and (iii) from Crop Subgroup 5B to Crop Subgroup 4-16B (*Brassica* Leafy Greens); and (4) Tolerance Expansions of Representative Commodities to (i) Cottonseed Subgroup 20C, and (ii) Stalk and Stem Vegetable Subgroup 22A, except Kohlrabi.

Kidwell, J. *et al*. 9/27/2018. D447125. S-metolachlor: Human Health Risk Assessment for (1) Establishment of Tolerances for New Uses on Chicory, Stevia and Swiss Chard; (2) Tolerance Translations from Table Beet Tops, Turnip Greens, and Radish Tops to Crop Group 2 (Leaves of Root and Tuber Vegetables), except Sugar Beets; (3) Tolerance Conversions (i) from Crop Subgroup 4B to Crop Subgroup 22B (Leaf Petiole Vegetable), (ii) from Crop Subgroup 5A to Crop Group 5-16 (*Brassica*, Head and Stem Vegetable) and (iii) from Crop Subgroup 5B to Crop Subgroup 4-16B (*Brassica* Leafy Greens); and (4) Tolerance Expansions of Representative Commodities to (i) Cottonseed Subgroup 20C, and (ii) Stalk and Stem Vegetable Subgroup 22A, except Kohlrabi.

Koper, C. 12/16/2014. D420047. Tier II Drinking Water Assessment for the Proposed S-Metolachlor Use on Lettuce (Head and Leaf), Low-Growing Berry Subgroup 13-07G (excluding Cranberry), Cucurbit Vegetable Group 9, Sunflower Subgroup 20B and Fruiting Vegetable Group 8-10.

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Van Deusen, B. 9/25/2018. D447124. S-metolachlor- Occupational and Residential Exposure Assessment for the Proposed Uses on stevia; leaves of root and tuber, group 2, except sugar beet; brassica, head and stem, group 5-16; brassica, leafy greens, subgroup 4-16B, except Chinese broccoli; leaf petiole vegetable subgroup 22B; stalk and stem vegetable subgroup 22A, except celtuce, Florence fennel, and kohlrabi; cottonseed subgroup 20C; swiss chard; celtuce; Florence fennel; kohlrabi; and Chinese broccoli.

Van Deusen, B. 9/6/2019. D452743. Metolachlor and S-Metolachlor**:** Occupational and Residential Exposure Assessment in Support of Registration Review.

Appendix A. Toxicology Profile, Executive Summaries and Literature Search

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for S-metolachlor/Metolachlor are listed in the Table below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used. Acceptable bridging studies for S-metolachlor include an Acute Toxicity Battery, subchronic toxicity studies in rats and dogs, developmental toxicity studies in rats and rabbits, mutagenicity battery, a metabolism study and an immunotoxicity study.

Study	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	yes	yes[a]
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes[b]
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes[c]	-
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes[c]	-
870.6300 Develop. Neurotoxicity	conditional[c]	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	yes
Special Studies for Ocular Effects Acute Oral (rat) Subchronic Oral (rat) Six-month Oral (dog)	no	

[a] HASPOC recommended the study be required. Study received. (Van Alstine, J., 03/20/2013, TXR 0056586)
[b] Satisfied with combined chronic toxicity/carcinogenicity study
[c]Recommended for a waiver by HASPOC (Van Alstine, J., 03/20/2013, TXR 0056586)

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Metolachlor				
Guideline No.	**Study Type**	**MRID #**	**Results**	**Toxicity Category**
870.1100	Acute Oral Toxicity – rat TXR No. 5000829	45433701	LD_{50} = 1063 mg/kg (Female) LD_{50} = 1936 mg/kg (Male) LD_{50} = 1425 mg/kg (Combined)	III
870.1200	Acute Dermal Toxicity - rabbit TXR No. 5000829	45433702	LD_{50} => 5050 mg/kg	IV
870.1300	Acute Inhalation Toxicity – rat TXR No. 5000829	45433703	LC_{50} => 2.02 mg/L	IV
870.2400	Acute Eye Irritation - rabbit TXR No. 5000829	45433704	Corneal opacity in 5/6 eyes at 1 hour, resolved by 48 hours. Conjunctivitis in 1 eye at 1 hour, resolved by 72 hours.	III
870.2500	Acute Dermal Irritation - Rabbit TXR No. 5000829	45433705	Minimal irritation	IV
870.2600	Skin sensitization – guinea pig TXR No. 0000434	00015631	Positive	NA

Table A.2.2 Acute Toxicity Profile – S-Metolachlor[a]				
Guideline No.	**Study Type**	**MRID #**	**Results**	**Toxicity Category**
870.1100	Acute Oral Toxicity – rat TXR No. 0012310	43928915	LD_{50} = 3267 mg/kg (Male) LD_{50} = 2577 mg/kg (Female) LD_{50} = 2672 mg/kg (Combined)	III
870.1200	Acute Dermal Toxicity - rabbit TXR No. 0012310	43928916	LD_{50} => 2000 mg/kg	III
870.1300	Acute Inhalation Toxicity – rat TXR No. 0012310	43928917	LC_{50} => 2.91 mg/L	IV
870.2400	Acute Eye Irritation - rabbit TXR No. 0012310	43928918	Slight to moderate conjunctival irritation that cleared in 48 hours	III
870.2500	Acute Dermal Irritation - Rabbit TXR No. 0012310	43928919	Non-irritating	IV
870.2600	Skin sensitization – guinea pig TXR No. 0012310	43928920	Positive (Buehler Method)	NA

Table A.2.3 Subchronic, Chronic and Other Toxicity Profile - Metolachlor			
Guideline No.	**Study Type/TXR Nos. or DP Barcode**	**MRID No. (year)/ Doses**	**Results/ Classification**
870.3100	90-Day oral (diet) toxicity (rat) (Metolachlor) D254363	44775401 (1999) 0, 30, 300, 3000 ppm (M/F: 0, 2.00/2.32, 20.2/23.4, 210/259 mg/kg/day)	NOAEL for males = 210 mg/kg/day LOAEL for males not established NOAEL for females = 23.4 mg/kg/day LOAEL for females = 259 mg/kg/day based on decreased body weight Acceptable/Guideline

Table A.2.3 Subchronic, Chronic and Other Toxicity Profile - Metolachlor			
Guideline No.	**Study Type/TXR Nos. or DP Barcode**	**MRID No. (year)/ Doses**	**Results/ Classification**
870.3150	6-Month oral (diet) toxicity (dog) (Metolachlor) TXR Nos. 0057763, 0010251	00032174 (1980), 43244001 (1994) 0, 100, 300, 1000 ppm (M/F: 0, 2.92/2.97, 9.71/8.77, 29.61/29.42)	NOAEL = 1000 ppm (29.61 mg/kg/day) (HDT) LOAEL = Not established Acceptable/Non-Guideline
870.3200	21-Day dermal toxicity rabbits (Metolachlor) TXR Nos. 0050330, 0009558, 0010315	41833101 (1987) 0, 10, 100 or 1000 mg/kg/day	Systemic NOAEL = 1000 mg/kg/day. Systemic LOAEL was not established Dermal irritation NOAEL was not established Dermal irritation LOAEL = 10 mg/kg/day based on very slight erythema, dry skin and fissuring (one animal) Acceptable/Guideline
870.3465	28-day Inhalation rat (Metolachlor) TXR No. 0057665	MRID 50410101 (2017) 0 (filtered air), 0.1, 0.3, 1.0 mg/L (0, 100, 300, 1000 mg/m^3)	Systemic NOAEC= 1.0 mg/L (1000 mg/m3, limit dose) LOAEC not determined Portal of Entry NOAEC = 0.1 mg/L (100 mg/m3) Portal of Entry LOAEC= 0.3 mg/L (300 mg/m^3) based on hyperplasia of the squamous epithelium and subacute inflammation in both sexes, and mucous cell hyperplasia in males at nasal level II. Acceptable/Guideline
870.3700a	Prenatal developmental toxicity in rodents (rat) (Metolachlor) TXR Nos. 0057763; 0050330; 0009509	00151941 (1985) 0, 30, 100, 300 or 1000 mg/kg/day	Maternal NOAEL = 300 mg/kg/day. Maternal LOAEL = 1000 mg/kg/day based on an increased incidence of death and clinical signs of toxicity (clonic and/or toxic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation). Developmental NOAEL = 1000 mg/kg/day (HDT) Developmental LOAEL = not established Acceptable/Guideline
870.3700b	Prenatal developmental in (New Zealand White) rabbits (Metolachlor) TXR Nos. 0057763; 0050330; 0001051; 0001088	00041283 (1980) 0, 36, 120 or 360 mg/kg/day	Maternal NOAEL was 360 mg/kg/day (highest dose tested). Maternal LOAEL was not established. Developmental toxicity NOAEL = 360 mg/kg/day Developmental toxicity LOAEL was not established. Acceptable/Guideline
870.3800	Reproduction and fertility effects (CD albino) rats	00080897 (1981) 0, 30, 300 or 1000 ppm F_0 males: 0, 2.4, 23.5,	**Parental/Systemic** NOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day) highest dose tested.

Table A.2.3 Subchronic, Chronic and Other Toxicity Profile - Metolachlor			
Guideline No.	**Study Type/TXR Nos. or DP Barcode**	**MRID No. (year)/ Doses**	**Results/ Classification**
	(Metolachlor) TXR Nos. 0057763, 0050330, 0010088	and 75.8 mg/kg/day; F_0 females: 0, 2.5, 26.0, and 85.7 mg/kg/day; F_1 males: 0, 2.3, 23.7, and 76.6 mg/kg/day; F_1 females: 0, 2.6, 25.7, and 84.5 mg/kg/day metolachlor (95.4% ai) (dietary)	LOAEL = Not established **Reproductive** NOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day highest dose tested. LOAEL = Not established **Offspring** NOAEL = 300 ppm (F_0 females: 26.0 mg/kg/day). LOAEL = 1000 ppm (F_0 females: 85.7 [~86] mg/kg/day highest dose tested based on decreased pup body weight in both sexes in F_1 and F_2 litters. Acceptable/Guideline
870.4100b	Chronic toxicity dogs (Metolachlor) TXR Nos. 0057763, 0050330, 0008442	40980701, 41164501, 42218601 and 42218602. (1989) 0, 100, 300 or 1000 ppm (males: 0, 3.5, 9.7 and 32.7 mg/kg/day, respectively; females: 0, 3.6, 9.7 and 33.0 mg/kg/day, respectively) for one year.	NOAEL = 1000 ppm (32.7/33.0 mg/kg/day, M/F). LOAEL for males/females was not established; Acceptable/Guideline
870.4200	Chronic toxicity/ Carcinogenicity Rat (Metolachlor) TXR Nos. 0057655, 0010251, 0001374	00129377 (1983) 0, 30, 300 or 3000 ppm (0, 1.5, 15 or 150 mg/kg/day based on 1 ppm in food equals 0.05 mg/kg/day)	NOAEL= 300 ppm (15 mg/kg/day), both sexes LOAEL = 3000 ppm (150 mg/kg/day), both sexes, based on decreased body weights and food consumption in the females, and increased liver weights in males, and non-neoplastic microscopic findings of foci of cellular alteration in the liver of the males and females. Treatment-related increases in liver tumors were seen at 3000 ppm in female rats. No treatment-related tumors were seen in male rats. Acceptable/Guideline
870.4300	Carcinogenicity Mice (Metolachlor) TXR Nos. 0050330, 0003885	00117597 (1982) 0, 300, 1000 or 3000 ppm (0, 45, 150 or 450 mg/kg/day)	NOAEL = 100 ppm (150 mg/kg/day) LOAEL = 3000 ppm (450 mg/kg/day) based on possible treatment-related deaths in females and decreased body weight/body weight gain in males and females. No evidence of carcinogenicity. Acceptable/Guideline
870.5100	Gene Mutation bacterial reverse mutation TXR No. 0006444	00015397 (1976) 10, 100, 1000 and 10,000 ug/plate	Negative up to cytotoxic doses (1000 ug/plate) Acceptable/Guideline

Table A.2.3 Subchronic, Chronic and Other Toxicity Profile - Metolachlor			
Guideline No.	**Study Type/TXR Nos. or DP Barcode**	**MRID No. (year)/ Doses**	**Results/ Classification**
870.5300	Gene Mutation mouse lymphoma TXR No. 0006444	00158929 (1984) 9.5-190 nL/mL without activation; 10.5-280 nL/mL with activation	No effect on the incidence of mutations in the presence or absence of metabolic activation Acceptable/Guideline
870.5395	Cytogenetics micronucleus assay in Chinese hamsters TXR No. 0004725	00158925 (1984) 0, 1250, 2500 or 5000 mg/kg	No effect of treatment on incidence of micronuclei induction Acceptable/Guideline
870.5450	Cytogenetics dominant lethal assay in mice TXR No. 0000434	00015630 (1978) 100 or 300 mg/kg	No effect on embryonic death, pre- and post-implantation or fertility rates in mated females Acceptable/Guideline
870.5550	Other Effects DNA Damage/Repair in rat hepatocytes TXR No. 0004725	00142828 (1984) 0.125, 0.625, 3.125 or 15.625 nL/mL	Negative Acceptable/Guideline
870.5550	Other Effects DNA Damage/Repair in human fibroblasts TXR No. 0004725	00142827 0.125, 0.625, 3.125 or 15.625 nL/mL	Negative Acceptable/Guideline
870.5550	Other Effects Unscheduled DNA synthesis in rat hepatocytes TXR No. 0011115	43244003 (1994) 1250, 2500 or 4000 mg/kg to males; 500, 1000 or 1500 mg/kg to females	Negative for induction of UDS; however, significant increases in percentage of cells in S-phase were observed in females dosed at 500 mg/kg (but not at 1000 or 1500 mg/kg) and sacrificed at 15 hours Acceptable/Guideline
870.7485	Metabolism and pharmacokinetics TXR No. 0010990	43164201 (1992) low oral dose (1.5 mg/kg x 14 days), and a single high dose (300 mg/kg)	Comparison of oral and intravenous data showed that of the administered dose, between 69.6% and 93.2% was absorbed. Distribution data showed that the only significant sites of residual radioactivity at 7 days post-dose were residual carcass (0.9 - 2.2% of the administered dose) and red blood cells (0.95- 1.53 µg equivalents/gram in blood cells for all low dose male and female rats). Dosing regimen did not result in any apparent accumulation of residual radioactivity. Excretion data showed that urine and feces were both significant routes for elimination of metolachlor derived radioactivity Metabolism of metolachlor in this study was complex, with up to 32 metabolites identified in urine and/or feces. Acceptable/Guideline

Table A.2.3 Subchronic, Chronic and Other Toxicity Profile - Metolachlor			
Guideline No.	**Study Type/TXR Nos. or DP Barcode**	**MRID No. (year)/ Doses**	**Results/ Classification**
870.7600	Dermal Penetration (Metolachlor) TXR No. 0050330, 0009558	41833102 (1987) 0, 0.01, 0.1, or 1.0 mg/cm2	An estimated dermal absorption factor (DAF) of 58% was determined based on combined values at 10 hour measurements (33%) and at the amount remaining on the skin (25%). The DAF of 58% is highly conservative because the animals were exposed to the test chemical for a full 24 hours, and the full amount remaining in the skin was included into the dermal absorption value because tape stripping was not conducted. Acceptable/Guideline
Non-Guideline Mode of Action Study	CGA24705 (Metolachlor)– Assessment of hepatic cell proliferation, apoptosis and liver enzyme induction in female rats upon treatment for up to sixty days. TXR No. 0057655	50396003 (2006) 0 or 3000 mg/kg for 3, 5, 7, 14, 28 and 60 days	The overall results of the investigation demonstrate, and reconfirm, that metolachlor is a strong and reversible hepatic enzyme inducer in rats. Treatment with metolachlor at a dietary dose of 3000 mg/kg resulted in increases of microsomal cytochrome P-450 concentration by Day 60 (↑30%), and increased activities of microsomal O-demethylation of methoxyresorufin (↑62%), O-deethylation of ethoxyresorufin (↑93%), O-dependentylation of pentoxyresorufin (↑1490%), and O-debenzylation of benzyloxyresorufin (1818%), as well as moderate increases in epoxide hydrolase, UDPGT, and cytosolic glutathione S-transferase up to Day 60. In addition, microsomal testosterone hydroxylation rates were increased most strongly at positions 16α (↑1117%) and 16β (↑1019%) by Day 60, with slight to moderate increases at most other hydroxylation positions (up to 200%), and immunoblot analyses indicated a strong increase of CYP2B1/2 proteins and a moderate increase of CYP3A1/2 proteins. These biochemical findings are generally aligned with treatment-related biochemical findings in a previous 28-day dietary toxicity study (Frankhauser, 1995, MRID 50396001; Persohn, 1995, MRID 50396002) with metolachlor and S-metolachlor under concurrent review.

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile – S-metolachlor			
Guideline No.	**Study Type/ TXR No.**	**MRID No. (year)/ Classification /Doses**	
870.3100	90-Day oral toxicity in rats TXR No. 0012310	43928923 (1995) 0, 30, 300, 3000 or 10000 ppm (0, 1.5, 15, 150 or 500 mg/kg/day)	NOAEL = 15 mg/kg/day (300 ppm) LOAEL = 150 mg/kg/day (3000 ppm) based on decreased body weights/body weight gains, reduced food consumption and food efficiency, and increased kidney weights Acceptable/Guideline

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile – S-metolachlor			
Guideline No.	**Study Type/ TXR No.**	**MRID No. (year)/ Classification /Doses**	
870.3100	90-Day oral toxicity in rats TXR No. 0050328	44775402 (1999) 0, 30, 300, 3000 ppm (M/F: 0, 1.90/2.13, 20.4/23.9 and 208.0/236.0 mg/kg/day0	NOAEL = 3000 ppm (equivalent to 208 mg/kg/day in males and 236 mg/kg/day in females LOAEL cannot be defined Unacceptable/Guideline
870.3150	90-Day oral toxicity nonrodents (dog) TXR No. 0012310	43928922 (1995) 0, 300, 500, 1000 or 2000 ppm (M/F: 0, 9/10, 15.1/17.2, 31.1/31.5 or 62/74 mg/kg/day)	NOAEL = 2000 ppm (M/F: 62/74 mg/kg/day) LOAEL = not established Acceptable/Non-guideline
870.3700a	Prenatal developmental in (Tif:RAI f (SPF)) rats TXR Nos. 0057763, 0012310	43928925 (1995) 0, 5, 50, 500, or 1000 mg/kg/day S-metolachlor (95.6% ai) in 0.5% (w/w) aqueous solution of sodium carboxymethylcellulose (gavage) GD 6-15	**Maternal** NOAEL= 1000 mg/kg/day. Maternal LOAEL = Not established. **Developmental** NOAEL = 1000 mg/kg/day, highest dose tested. LOAEL = Not established Acceptable/Guideline
870.3700b	Prenatal developmental in (New Zealand White) rabbits TXR No. 0012310	43928924 (1995) 0, 20, 100, or 500 mg/kg/day S-metolachlor (89.6% ai (93.7% S isomer)) suspension in 3% corn starch (gavage) GD 7-19	Maternal NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on clinical signs of toxicity (little/none/soft stools). Developmental NOAEL = 500 mg/kg/day, highest dose tested. LOAEL = Not established Acceptable/Guideline
870.5100	Gene Mutation Salmonella & Escherichia/Mammalian Microsome Mutagenicity Test TXR No. 0012310	43928927 (1995) 78.13-1250.0 ug/plate	In independently performed microbial mutagenicity assays, *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102 and *Escherichia coli* WP2 *uvr*A were initially exposed to 312.5-5000.0 µg/plate CGA-77102 technical (95.6%) in the presence and absence of S9 activation. For the confirmatory trial, doses of 78.13-1250.0 µg/plate ±S9 were evaluated with *S. typhimurium* strains TA1535, TA1537, TA100 and TA102; concentrations of 312.5-5000.0 µg/plate ±S9 were examined with *S. typhimurium* TA 98 and *E.coli* WP2 *uvr*A. In general, doses ≥1250.0 µg/plate ±S9 were cytotoxic for *S. typhimurium* TA1535, TA1537, TA100 and TA102 and 5000.0 µg/plate ±S9 was slightly cytotoxic for *S. typhimurium* TA98 and *E. coli* WP2 uvrA. There was, however, no indication that CGA-77102 technical induced of a mutagenic effect in any tester strain either in the presence or the absence of S9 activation. Acceptable/Guideline

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile – S-metolachlor			
Guideline No.	**Study Type/ TXR No.**	**MRID No. (year)/ Classification /Doses**	
870.5395	Cytogenetics Micronucleus test TXR No. 0012310	43928926 (1995) 500, 1000 or 2000 mg/kg	Groups of five male and five female Tif:MAGf(SPF) mice received single oral gavage administrations of 500, 1000 or 2000 mg/kg CGA 77102 technical (95.6%). Toxic signs, similar to those seen in the preliminary range-finding studies (i.e., ataxia, tremors and/or hunched posture) were recorded for high-dose males and females throughout the 48-hour postexposure. No bone marrow cytotoxicity was seen at any dose or sacrifice time. The positive control induced the expected high yield of MPEs in males and females. There was, however, no evidence that CGA 77102 technical induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time. Acceptable/Guideline
870.5550	Other Effects Unscheduled DNA synthesis TXR No. 0012310	43928928 (1995) 500, 1500, 3200 (females), 5000 (males) mg/kg	CGA 77102 Technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this in vivo/in vitro rat hepatocyte RDS/UDS assay. Acceptable/Guideline
870.7485	Metabolism and pharmacokinetics TXR No. 0050329	44491401 (1996) single dose of 0.5 (group B1) or 100 mg/kg (group D1) radiolabeled CGA-77102; 100 mg/kg/day non-radiolabeled CGA 77102 for 14 days followed by 0.5 mg/kg radiolabeled CGA-77102 (Group V1); single dose of 0.5 or 100 mg/kg radiolabeled CGA-77102 for bile-cannulation study	In all three dose groups (B1, D1, and V1), the seven day combined levels of radioactivity in urine were 31.1 - 36.5% for males and 40.8 - 45.5% for females; the fecal levels were 60.2 - 62.5% for males and 48.9 - 55.0% for females. Only 0.1% or less was eliminated in the expired air. The total recovery ranged from 96.5 ± 2.3% to 99.3 ± 0.9%. Irrespective of the dose and sex, there seems to be a biphasic plasma profile with two concentration maxima (C_{max}); a fast rising first C_{max} was reached at 0.25 - 1 hour post dosing which was succeeded by a second C_{max} at 8 and at 12 - 24 hours following administration of the low and high dose, respectively. Acceptable/Guideline
870.7800	Immunotoxicity in mice TXR No. 0056377	48783301 (2012) 0, 1500, 3000 or 5000 ppm (0, 304.3, 639.5, or 1108.5 mg/kg/day)	NOAEL = 5000 ppm (1108.5 mg/kg/day) LOAEL = Not Established Acceptable/Guideline
Non-Guideline Mode of Action Study	S-metolachlor Enzyme and DNA Synthesis Induction in Cultured Female Human Hepatocytes TXR No. 0057655	49927702 (2014) Main Study 49927703 (2014) Range Finding Study Main: 0, 1, 5, 10, 20, 40, or 75 µM for 96 h. Range Finding: 0, 5, 10, 20, 40, 75, 150, 300, 450, or 600 µM for 96 h.	In main study, S-metolachlor treatment resulted in cytotoxicity at 40 and 75 µM, but did not induce DNA synthesis or enzyme activity at any concentration tested under the conditions of this study. The cultured female human hepatocytes responded as expected to the positive controls for DNA synthesis (EGF) and enzyme induction (PB). Acceptable/Non-guideline

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile – S-metolachlor			
Guideline No.	**Study Type/ TXR No.**	**MRID No. (year)/ Classification /Doses**	
Non-Guideline Mode of Action study	S-metolachlor – enzyme and DNA synthesis induction in cultured female rat hepatocytes. TXR No. 0057655	49927704 (2014) Main Study 49927705 (2014) Range Finding Study Main: 0, 1, 5, 10, 20, 40, or 75 µM for 96 h. Range Finding: 0, 5, 10, 20, 40, 75, 150, 300, 450, or 600 µM for 96 h	S-metolachlor treatment decreased intracellular ATP levels in the 75 µM group, indicating cytotoxicity at this concentration. Treatment with S-metolachlor at ≥1 µM caused consistent increases in the BrdU labeling index indicating induction of DNA synthesis, although strict dose-dependency was not observed. There were no effects of S-metolachlor treatment on PROD activity. Treatment with S-metolachlor at ≥10 µM caused increases in BROD activity indicating induction of CYP 2B/3A, although strict dose-dependency was not observed. Acceptable/Non-Guideline
Non-Guideline Mode of Action Study	Oral (dietary) 14-day mechanistic study to evaluate effects on the liver in the female rat TXR No. 0057655	49927706 (2014) 0, 300, 3000, or 5000 ppm (equivalent to 0, 32.2, 303.1, and 536.4 mg/kg/day)	An increase in the BrdU labeling index (# BrdU labeled cells/1000 cells) was observed at 3000 ppm on Days 2, 3, and 4 and at 5000 ppm on Days 2 and 4. The BrdU labeling index was similar to control levels on Days 8 and 15. Hepatic microsomal protein levels were increased ($p<0.05$) by 13% at 3000 ppm on Day 15, and by 14-25% at 5000 ppm on Days 4, 8, and 15. PROD and BROD activities generally increased with dose. PROD activity was increased ($p<0.01$) as follows: 404-1159% at 3000 ppm on Days 2, 3, 4, 8, and 15; and 679-1629% at 5000 ppm on Days 2, 3, 4, 8, and 15. BROD activity was increased as follows: 457-2816% at 3000 ppm on Days 2, 3, 4, 8, and 15; and 992-2618% at 5000 ppm on Days 2, 3, 4, 8, and 15. Acceptable/Non-Guideline
Non-Guideline Mode of Action Study	CAR3 transactivation assay with mouse, rat, and human CAR TXR No. 0057655	49927707 (2014) 1, 3, 10, or 30 µM	S-metolachlor activated the CAR3 constructs in a dose-dependent manner. Human CAR3 was activated by 2.8- to 8.7-fold at concentrations ≥3 µM; mouse CAR3 was activated by 8.5- to 26.9-fold at concentrations ≥1µM; and rat CAR3 was activated by 51.3- to 57.1-fold at concentrations ≥10µM. Acceptable/Non-Guideline

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile – S-metolachlor			
Guideline No.	**Study Type/ TXR No.**	**MRID No. (year)/ Classification /Doses**	
Non-Guideline Mode of Action Study	CGA24705 and CGA77102 – 28 days subacute, oral toxicity study in rats (administration in food). TXR No. 0057655	50396001 (1995) 0, 30, 300, 3000, or 5000 ppm (S-metolachlor mean daily intake: 0, 2.65, 24.5, 242, and 426 mg/kg bw/day and 0, 2.73, 26.4, 257, 435 mg/kg bw/day for males and females, respectively; metolachlor mean daily intake[13]: 265 and 447 mg/kg bw/day for groups 4 and 5 males, respectively, and 264 and 433 mg/kg bw/day for groups 4 and 5 females, respectively) for up to four weeks.	This non-guideline 28-day study is considered supplemental information, although it was considered acceptable for regulatory purposes. This study, in conjunction with MRID 50396002, is being used to support a cancer mode-of-action for liver tumors with the intended purpose of comparing the effects of treatment with metolachlor (CGA24705) to those of S-metolachlor (CGA77102) in rats. This non-guideline 28-day study is considered supplemental information, although it was considered acceptable for regulatory purposes. This study, in conjunction with MRID 50396002, is being used to support a cancer mode-of-action for liver tumors with the intended purpose of comparing the effects of treatment with metolachlor (CGA24705) to those of S-metolachlor (CGA77102) in rats.

[13] Mean daily intake for groups 2 and 3 could not be calculated due to technical error.

Table A.2.4 Subchronic, Chronic and Other Toxicity Profile – S-metolachlor			
Guideline No.	**Study Type/ TXR No.**	**MRID No. (year)/ Classification /Doses**	
Non-Guideline Mode of Action Study	CGA24705 (Metolachlor) and CGA77102 (S-metolachlor) – Assessment of replicative liver DNA synthesis and effects on selected ultramorphological and biochemical liver parameters in the course of a 28-day subacute, oral toxicity study in male and female rats TXR No. 0057655	50396002 (1995) metolachlor (CGA24705) or S-metolachlor (CGA77102, in the diet at dose levels of 0 (13 rats/sex), 30 (8 rats/sex), 300 (8 rats/sex), 3000 (13 rats/sex), or 5000 (13 rats/sex) mg/kg for up to 28 days.	The overall results of the present investigation demonstrate that metolachlor and S-metolachlor are strong and reversible hepatic enzyme inducers in male and female rats. Treatment with metolachlor and S-metolachlor at dietary doses of 3000 and 5000 mg/kg resulted in increases of microsomal cytochrome P-450 content (approximately 30-60%), and increased activities of microsomal EROD (approximately 100-900%), PROD (approximately 100-6000%), and UDPGT (approximately 40-160%). The ultramorphological and biochemical findings are aligned with treatment-related findings in the 28-day dietary toxicity study (Frankhauser, 1995; MRID 50396001) of increased liver weights and centrilobular hypertrophy. Further study results demonstrated that metolachlor and S-metolachlor did not induce replicative DNA synthesis in hepatocytes, and they did induce microsomal CYP3A or CYP4A levels. This non-guideline 28-day study is considered supplemental information, although it was considered acceptable for regulatory purposes. This study, in conjunction with MRID 50396001, is being used to support a cancer mode-of-action for liver tumors with the intended purpose of comparing the effects of treatment with metolachlor (CGA24705) to those of S-metolachlor (CGA77102) in rats.

Table A.2.5 Subchronic, Chronic and Other Toxicity Profile - Metabolites			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral (diet) toxicity (rat) (CGA 354743 [metolachlor ESA, degradate of metolachlor]) TXR No. 0050330	44931710 (1999) 0, 360, 1200, 6000, or 20,000 ppm M/F:(25.1/28.4, 86.2/98.3, 427/519, 1545/1685 mg/kg/day	NOAEL is 20,000 ppm (1543/1685 mg/kg/day, M/F). LOAEL was not established. Acceptable/Guideline
870.3100	90-Day oral (diet) toxicity (rat) (CGA 51202 [metolachlor OA, degradate of metolachlor]) TXR No. 0050330	44929509 (1992) 0, 300, 1000, or 15,000 ppm M/F: 0/0, 18.7/20.6, 62.1/67.3 , 1000/1020 mg/kg/day	NOAEL = 15,000 ppm (1000/1020 mg/kg/day, M/F) LOAEL was not established. Acceptable/Guideline
870.3150	90-day oral (capsule) toxicity (dog) (CGA 354743, metabolite of metolachlor) TXR No. 0050330	44931709 (1999) 0, 50, 200, 500, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (highest dose tested) LOAEL was not established. Acceptable/Guideline
870.3700a	Prenatal developmental toxicity in rodents (rat) (CGA 354743, metabolite of metolachlor) TXR No. 0050330	44931711 (1999) 0, 250, 500, 1000 mg/kg/day	Maternal NOAEL = 1000 mg/kg/day Maternal LOAEL not identified. Developmental NOAEL = 1000 mg/kg/day Developmental LOAEL not identified. Acceptable/Guideline
870.3700a	Prenatal developmental toxicity in rodents (rat) (CGA 51202, metabolite of metolachlor) TXR No. 0050330	44929510 (1992) 0, 10, 100, 1000 mg/kg/day	Maternal NOAEL = 1000 mg/kg/day Maternal LOAEL not identified. Developmental NOAEL = 1000 mg/kg/day Developmental LOAEL not identified. Acceptable/Guideline

A.3 Hazard Identification and Endpoint Selection

A.3.1/A.3.2 Acute Reference Dose (aRfD) – General Population and Females age 13-49

An acute dietary assessment for all populations is not required. The adverse effects resulting from a single dose in the developmental rat study with metolachlor occurred at the limit dose of 1000 mg/kg/day, which is a dose that is not relevant for risk assessment. In addition, an endpoint was not selected for Females 13-49 years old since no developmental effects attributable to a single exposure were identified in the metolachlor/S-metolachlor database.

A.3.3 Chronic Reference Dose (cRfD) – All Populations

Study Selected: 2-Generation Reproduction Toxicity Study in Rats
MRID No.: 00080897
Executive Summary: See Appendix A, Guideline [§ 870.3800]
Dose and Endpoint for Risk Assessment: Offspring NOAEL = 26 mg/kg/day based on decreased pup weight in F1 and F2 litters seen at offspring LOAEL = 86 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: The 2-generation reproduction study in rats with metolachlor (MRID 00080897) was selected for the chronic dietary endpoint for the general population. The POD is the offspring NOAEL of 26 mg/kg/day. The offspring LOAEL is 86 mg/kg/day based on decreased pup body weight in F1 and F2 litters on lactation days (LDs) 4, 7, 14, and 21. This study is appropriate for the route of exposure (oral) and the population of concern. It is protective of the quantitative susceptibility seen in this study (i.e., decreased pup body weight occurred in the absence of maternal toxicity). The POD selected is protective of the effects seen at this dose as well as of the effects seen in the chronic toxicity/carcinogenicity study. It is appropriate for this duration of concern and is protective of all populations. An UF of 100 was applied to account for interspecies extrapolation (10X), intraspecies variability (10X) and the FQPA Safety Factor of 1X. The cRfD is equal to the cPAD of 0.26 mg/kg/day. The cPAD is protective of chronic toxicity, including carcinogenicity, that could result from exposure to metolachlor/S-metolachlor.

A.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: 2-Generation Reproduction Toxicity Study in Rats
MRID No.: 00080897
Executive Summary: See Appendix A, Guideline [§ 870.3800]
Dose and Endpoint for Risk Assessment: Offspring NOAEL = 26 mg/kg/day based on decreased pup weight in F1 and F2 litters seen at offspring LOAEL = 86 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: The 2-generation reproduction study in rats with metolachlor (MRID 00080897) was selected for the incidental oral endpoint. The POD is the offspring NOAEL of 26 mg/kg/day. The offspring LOAEL is 86 mg/kg/day based on decreased pup body weight in F1 and F2 litters on lactation days (LDs) 4, 7, 14, and 21. This study is appropriate for the route of exposure (oral) and the population of concern (children). The POD is protective of the quantitative susceptibility seen in this study (i.e., decreased pup body weight occurred in the absence of maternal toxicity). An uncertainty factor of 100X was applied to endpoints selected for the oral exposure route (10X for interspecies extrapolation, 10X for

intraspecies variation, and 1X FQPA SF). The residential level of concern for the margin of exposure (MOE) is 100.

A.3.5 For Children - Dermal Exposure (Short- and Intermediate-Term)

Study Selected: 2-Generation Reproduction Toxicity Study in Rats
MRID No.: 00080897
Executive Summary: See Appendix A, Guideline [§ 870.3800]
Dose and Endpoint for Risk Assessment: NOAEL = 26 mg/kg/day based on decreased pup weight in F1 and F2 litters seen at LOAEL = 86 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: A route-specific 21-day dermal toxicity study in rabbits with metolachlor (MRID 41833101) is available and produced no adverse systemic effects up to the limit dose of 1000 mg/kg/day. However, quantitative susceptibility has been identified in the rat 2-generation reproduction study (i.e., decreased pup body weight occurred in the absence of maternal toxicity). Since the 28-day dermal study is not designed to evaluate offspring toxicity by the dermal route it was not selected for risk assessment. Therefore, the 2-generation reproduction toxicity study in the rat was selected for the dermal endpoint to be protective of this susceptibility. The total Uncertainty Factor is 100X (10X for inter-species, 10X for intra-species extrapolation, and 1X FQPA SF). As discussed in Section 4.1.2, the dermal absorption factor for this risk assessment is 58%. The offspring NOAEL/LOAEL in this study is an oral dose of 26/86 mg/kg/day, respectively, with an estimated dermal absorption factor of 58%. Using this dermal absorption factor, the dermal equivalent NOAEL/LOAEL would be 45/148 mg/kg/day which is below the dermal limit dose of 1000 mg/kg/day for assessing dermal risk. It is appropriate for the exposure duration and population of concern (children).

A.3.6 Adult - Dermal Exposure (Short-, Intermediate- and Long-Term)

A dermal assessment is not required since no systemic effects were seen up to the limit dose of 1000 mg/kg/day in a 21-day dermal toxicity study in rabbits with metolachlor. In addition, the quantitative susceptibility seen in the offspring in the 2-generation reproduction study is not relevant for adults.

A.3.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Study Selected: 28-Day Inhalation Toxicity Study in Rats
MRID No. 50410101
Executive Summary: See Appendix A, Guideline [§ 870.3465]
Dose and Endpoint for Risk Assessment: The portal of entry NOAEC is 0.1 mg/L (equivalent to 100 mg/m3). The portal of entry LOAEC is 0.3 mg/L (300 mg/m^3) based on hyperplasia of the squamous epithelium and subacute inflammation in both sexes, and mucous cell hyperplasia in males at nasal level II.
Comments about Study/Endpoint/Uncertainty Factors: A route-specific 28-day inhalation toxicity study in rats (MRID 50410101) was used for the short- and intermediate-term inhalation endpoint. This route specific study is appropriate for the duration and population of concern. For non-occupational scenarios, it provides a lower POD (Human Equivalent Doses) than the 2-

generation reproduction study and is, therefore, protective of quantitative susceptibility seen in that study. See human equivalent doses in Table 4.5.4.3. The non-occupational and occupational level of concern is 30X (3x for interspecies extrapolation, 10x for intraspecies variation, 1x FQPA SF). The database uncertainty factor of 10X that was previously required for the lack of an inhalation toxicity study in no longer relevant.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

In a 3-month dietary toxicity study (MRID 44775401), groups of male and female Sprague-Dawley rats (20/sex for controls, 10/sex/ treated group) were given CGA-24705 (Metolachlor) (a.i. 97.7 %, Lot/Batch P.111072) administered in feed at 0, 30,300 or 3000 ppm (equivalent to 0, 2.00, 20.2 and 210 mg/kg/day for males and 0, 2.32, 23.4 and 259 mg/kg/day for females).

No treatment-related deaths or clinical signs occurred during the study. In addition, there were no treatment-related effects on ophthalmologic parameters, water consumption, urinalysis, food efficiency or pathology in either males or females. There was no evidence of any treatment-related effect in males.

Decreased body weights were observed in females given 300 ppm and 3000 ppm CGA-24705; however, decreases in the 300 ppm group were not considered toxicologically significant due to the small magnitude of the effect. Decreases in the 30 and 300 ppm females was not considered toxicologically significant due to the lack of statistical significance and no dose-response effect. Statistically decreased food consumption was reported in 30, 300 and 3000 ppm females during Week 1 and in the 30 and 300 ppm group throughout the study. Overall mean food consumption was statistically decreased in 30, 300 and 3000 ppm females (-11 %, -11 % and -12%). The toxicological effect of treatment on food consumption is questionable as there was no dose-responsive effect and food efficiency was not affected.

Changes in a number of hematologic and clinical chemistry parameters were observed in female animals at all dose levels during the study; however, the toxicological significance is questionable due to the lack of a dose-response and the small magnitude of the effect. Statistically significant changes in absolute and relative organ weights were limited to decreased liver weight in 30 and 300 ppm females (-11 % and -12%, respectively), increased liver/body weight in 3000 ppm females (+9), and increased kidney/body weight in 30,300 and 3000 ppm females (+9%, + 11 % and + 13%, respectively). These effects are not considered toxicologically significant due to the small magnitude and the lack of accompanying histopathology changes.

The LOAEL for female Sprague-Dawley rats was 3000 ppm (259 mg/kg/day) based on decreased body weight. The NOAEL for females was 300 ppm (23.4 mg/kg/day). The LOAEL for male Sprague-Dawley rats was not established. The NOAEL for males was 3000 ppm (210 mg/kg/day).

This study is classified as Acceptable/Guideline [OPPTS 870.3100 (§82-la)] and satisfies the guideline requirements for a subchronic oral toxicity study in rodents.

870.3100 90-Day Oral Toxicity - Rat

In a 90-day subchronic oral toxicity limit study (MRID 44931710), groups of 10 male and 10 female Crl: CD BR rats were given CGA-354743 (Metolachlor ESA, degradate of metolachlor) (Lot/Batch # KI-5408/6, 98% a.i.) administered in the diet at concentrations of 0, 360, 1200, 6000, or 20,000 ppm. These concentrations were equivalent to 0, 25.1, 86.2, 427.0 or 1545.0 mg/kg/day for males and 0, 28.4, 98.3, 519.0 and 1685.0 mg/kg/day for females. An additional 10 male and 10 female rats were given CGA-77102 (S-metolachlor) (Lot/Batch # P.501001, 98.5% a.i.) administered in the diet at 5000 ppm (equivalent to 429 mg/kg/day for males and 563 mg/kg/day for females). The study was designed to assess the subchronic oral toxicity of CGA-354743 technical and to compare its toxic effects with those of its parent compound, CGA-77102 technical.

No deaths or clinical signs of toxicity occurred during this study. In addition, no statistically significant changes in body weight, body weight gain, food consumption, food efficiency, ophthalmologic examination, urinalysis, or histopathology was reported for animals fed CGA-354743. Limited and sporadic statistically significant changes in hematology, clinical chemistry, water intake and organ weight data were not dose-dependent, and were of questionable toxicological and biological importance.

Dietary exposure to CGA-77102 produced a statistically significant decreased body weight gain (-20%, $p \leq 0.01$) in males during week 1 only. Females exposed to CGA-77102 showed decreased body weight gain (-19%) by week 13, but these changes were not statistically significant. The food efficiency of rats fed CGA-77102 was decreased relative to their respective control animals. Male and female rats had increased absolute and relative liver weights. These results are consistent with a mild liver hypertrophy in females.

Based on the data presented in this study, the NOAEL is ≥20,000 ppm (1543 mg/kg/day and 1685 mg/kg/day for females) for CGA-354743. A LOAEL could not be established.
At 5000 ppm (429 mg/kg/day in males and 563 mg/kg/day in females) CGA-77102, there evidence of decreased body weight gain and food efficiency, increased absolute and relative liver weights and an increased incidence of hepatic centrilobular hypertrophy, although the effects were mild.

This subchronic oral toxicity study in rats is classified as Acceptable/Guideline [OPPTS 870.3100 (§82-1a)] and satisfies the guideline requirements.

870.3100 90-Day Oral Toxicity – Rat

In a subchronic oral feeding study, (MRID 44929509), CGA-51202 technical (Metolachlor OA, degradate of metolachlor) (100% a.i.; batch No. JD 7069/3) was fed to groups of 10 male and 10 female albino rats at dose levels of 0, 300, 1000, or 15,000 ppm for 3 months. The average

achieved doses for the corresponding groups were 0, 18.7, 62.1, and 1000 mg/kg bodyweight for males, and 0, 20.6, 67.3, and 1020 mg/kg for females.

All animals survived to study termination and no treatment-related clinical signs were observed. There were no treatment-related effects on body weight, food consumption, ophthalmoscopic parameters, or urinalysis. Platelet counts were decreased 16% ($p<0.01$) in high-dose males. Total protein in high-dose males (5% decrease, $p<0.01$) and females (4% decrease, N.S.) was slightly decreased due to decreased globulin in males and decreased albumin and globulin fractions in females. These effects were not considered biologically significant. There were no treatment-related organ weight effects or macroscopic or microscopic lesions. Under the conditions of this study, the NOAEL is 15,000 ppm in the diet (1000 mg/kg for males, 1020 mg/kg for females, limit dose) based on no biologically significant effects. A LOAEL was not identified.

This subchronic toxicity study in rats (82-1) is classified as Acceptable/Guideline. It satisfies the guideline requirement for a subchronic dietary toxicity study in rodents.

870.3100 90-Day Oral Toxicity – Rat

In a subchronic oral study (MRID 43928923), Sprague-Dawley rats (Strain: Crl: COBS® CD® (SD)BR from Source: Charles River Breeding Laboratories, Kingston, New York) received either 0, 30, 300, 3000, or 10000 ppm CGA-77102 Technical (Purity: 89.6% Dual content (93.7% S-Isomer); Batch No.: FL-830813 (SL-649)) in the diet for 13 weeks.

Treatment related systemic toxicity was noted at 3000 ppm and above as lower body weights and body weight gains in both sexes along with lower food consumption and reduced food efficiency. The 3000 and 10000 ppm males had increased absolute and relative kidney weights (statistically significantly different), this was a trend in the females also but only the relative organ weights were statistically significantly different. The 10000 ppm dose groups had increased gamma-GT activities and the males alone had increased eosinophilic intracytoplasmic inclusions bodies (of unknown etiology). The Systemic Toxicity NOAEL was 300 ppm and the LOAEL was 3000 ppm based on lower body weights and body weight gains, reduced food consumption and reduced food efficiency in both sexes and increased kidney weights in males.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements (§82-1a) for a subchronic feeding study in rats.

870.3150 90-Day Oral Toxicity - Dog

CGA-24705 (metolachlor) was administered at dose levels of 0, 100, 300, and 1000 ppm (0/0, 2.92/2.97, 9.71/8.77, 29.61/29.42 mg/kg/day, M/F) in the diet to Beagle dogs for 6 months (MRID 00032174). The 100- and 300- ppm dose levels were administered to 6 male and 6 female dogs and the 1000 ppm dose level was administered to 8 male and 8 female dogs. The control group also composed of 8 male and 8 female dogs received the basal diet without the test material. The extra dogs in the control and high dose groups represented recovery animals which

were maintained on only the basal diet for an additional month of the study. The dogs were observed daily for mortality and clinical signs. Individual body weights and food consumption were obtained and recorded weekly. Eye exams were performed in the pretest and at 6 months. Hematology and clinical chemistry were conducted once in the pretest and monthly thereafter. Urinalysis was performed once in the pretest period and at 2, 4, and 6 months of the study. Hematology, clinical chemistry and urinalysis were conducted for recovery dogs at 7 months of the study.

An effect was noted on the APTT in the mid and high dose males and females (not statistically significant in high dose females) at the end of the study; however, the biological relevance of these observations is unknown. Also, a statistically significant increase in alkaline phosphatase activity was noted in the mid dose males and high dose males and females, again the biological relevance of this observation is unknown as it is not accompanied by gross or histopathological observations. Reduced body weight was noted in the high dose males at 13 weeks (↓10.6%) and 26 weeks (↓12.7%). These effects were not corroborated in the chronic dog study. There were no effects on body weight in either sex seen in the chronic study at 13, 26, 32 or 52 weeks at 1000 ppm. Since these effects were not corroborated in the longer-term study, the decreased body weight in males seen in the subchronic dog study were considered to spurious and not adverse.

This study is acceptable as a range finding study for a subchronic toxicity study in the dog. The NOAEL= 1000 ppm (29.61 mg/kg/day), the highest dose tested. The LOAEL was not established.

The study is classified as **Acceptable/Non-guideline** and **does not satisfy** the guideline requirements for a subchronic toxicity study in dogs (OPPTS 870.3150).

870.3150 90-Day Oral Toxicity - Dog

In a subchronic oral study (MRID# 43928922), male and female beagle dogs (Source: Marshall Farms, North Rose, NY.) received either 0, 300, 500, 1000, or 2000 ppm S-metolachlor (CGA-77102 Technical) (95.4% purity; Lot Number FL-941255) in the diet or by capsule for 16 weeks. According to the investigators: "This study was initially designed to determine the toxicity of CGA-77102 via dietary exposure. However, during the first two weeks, very poor test diet consumption accompanied by weight loss were seen in both sexes given the top feeding level, 2000 ppm; the effect was worse in the females. Addition of corn oil or water to the test diet of the 2000-ppm females did not improve the palatability. Consequently, a decision was made to provide the test material orally to the high dose males and females via capsules; the daily dose (700 mg/dog) was calculated on the basis that all 350 grams of the test diet was consumed by each dog daily. Upon the initiation of capsule dosing, the 2000-ppm animals were switched to basal diet whereas the other dose groups continued to receive test diets. Because very little test diet was consumed by the 2000-ppm animals during the first two weeks, the whole duration of the study was extended by an additional three weeks to allow for a total of 14 weeks in capsule dosing and 16 weeks in test diet exposure. The overall study is best described as a 14/16 week oral/dietary study."

Other than the palatability problems noted above in the 2000 ppm dose group, no biologically relevant treatment related systemic toxicity was noted at any dose level tested. The Systemic Toxicity NOAEL was equal to or greater than 2000 ppm (62 mg/kg/day for males and 74 mg/kg/day for females) and the LOAEL was greater than 2000 ppm (62 mg/kg/day for males and 74 mg/kg/day for females).

This study is classified as Acceptable/Nonguideline and dose not satisfy the guideline requirements (§82-1b) for a subchronic feeding study in non-rodents.

870.3200 21/28-Day Dermal Toxicity – Rabbit

In a 21-day dermal toxicity study (MRID 41833101), metolachlor (96.4% a.i.) was applied topically once daily for 21 days to the intact skin of five New Zealand rabbits/sex/group at doses of 0, 10, 100 or 1000 mg/kg/day. All animals survived the treatment. There were no treatment-related effects on clinical signs, body weight/body weight gain, food consumption, ophthalmoscopic examinations, hematology or necropsy examinations. Significant increases in total bilirubin were observed only in females treated at 100 mg/kg/day (68% increase) and 1000 mg/kg/day (72% increase). However, these increases were not considered toxicologically significant as there was no other evidence of organ effects at these doses and hyperbilirubinemia has not been reported in other toxicity studies with metolachlor. Absolute and relative liver weight were significantly increased in the 1000 mg/kg/day males and relative kidney weight was significantly increased in 1000 mg/kg/day females. These effects are not considered toxicologically significant as there were no accompanying laboratory or necropsy findings.

There was evidence of skin irritation in all treated groups. Very slight erythema and dry skin were observed in all animals of the 10 mg/kg/day group; one female at this dose had fissuring. With increasing doses, more animals were observed to have fissuring and wrinkling of the skin. On histopathology, hyperkeratosis, parakeratosis, congestion of the dermis, edema and subacute lymphocytic infiltration were reported in some or all of the treated animals.

The systemic LOAEL was not established. The NOAEL was 1000 mg/kg/day (HDT).

The dermal irritation LOAEL was 10 mg/kg/day (LDT) based on very slight erythema, dry skin and fissuring (one animal). The NOAEL was not established.

The study is classified as acceptable/guideline and satisfies the guideline requirements for a 21-day dermal toxicity study in rabbits (82-2; OPPTS 870.3200).

870.3465 90-Day Inhalation – Rat

In a 4-week study, nose-only, inhalation toxicity study (MRID 50410101), groups of ten Crl:CD(SD) rats/sex/concentration were exposed to metolachlor (97.4% a.i.; Batch # BN160526) by nose only inhalation at concentrations of 0 (filtered air), 0.1, 0.3, or 1.0 mg/L (equivalent to 0, 100, 300, and 1000 mg/m^3) for six hours/day, five days/week for a total of 20-21 days. There was no recovery group.

There were no effects of treatment on mortality, clinical signs, body weight, food consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights, or gross pathology.

The systemic No Observed Adverse Effect Concentration (NOAEC) is 1.0 mg/L (equivalent to 1000 mg/m^3, limit dose). The Lowest Observed Adverse Effect Concentration (LOAEC) was not determined.

Portal-of-entry effects were noted in the nasal cavity. At 0.3 mg/L at nasal level II, minimal to mild hyperplasia of the squamous epithelium and subacute inflammation were observed in both sexes, and minimal to mild mucous cell hyperplasia was noted in the males. At 1.0 mg/L at nasal level II, minimal to mild hyperplasia of the respiratory epithelium, hyperplasia of the squamous epithelium, squamous metaplasia, mucous cell hyperplasia, and subacute inflammation were noted in both sexes. Additionally, at nasal level III, minimal to mild hyperplasia of the respiratory epithelium, hyperplasia of the squamous epithelium, and subacute inflammation were noted in both sexes, and mucous cell hyperplasia was recorded in the males.

The portal of entry LOAEC is 0.3 mg/L (300 mg/m^3) based on findings of hyperplasia of the squamous epithelium and subacute inflammation in both sexes, and mucous cell hyperplasia in the males observed at nasal level II. The portal of entry NOAEC is 0.1 mg/L (equivalent to 100 mg/m^3).

This study is classified Acceptable/Guideline. It satisfied the guideline requirements of OPPTS 870.3465: 90-day Inhalation Toxicity Study (with exception that duration of the study was 4 weeks instead of 90 days).

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID 00151941), CGA-24705 (metolachlor) (96.4% a.i., lot #B-203-004-A) in 0.5% (w/v) aqueous methyl cellulose was administered to 25 pregnant Crl:COBS®CD®(SD) BR female rats/dose by oral gavage (10 ml/kg) at dose levels of 0, 30, 100, 300 or 1000 mg/kg bw/day from days 6 through 15 of gestation. The animals were sacrificed on gestation day (GD) 20 and the fetuses were examined for evidence of developmental effects.

Administration of 1000 mg/kg/day resulted in the death of four of the 25 rats in this dosage group. These deaths occurred after the rats had been given seven (one rat died on GD12), eight (one rat died on GD 13) or ten (two rats died on GD15) consecutive daily doses. Three of the four rats which died were pregnant and died on days 12 through 15 of gestation. Clinical signs of toxicity, including clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation, were observed in animals treated at 1000 mg/kg/day. The excessive salivation and lacrimation, as well as the clonic and/or tonic convulsions was first noted beginning on first and/or second day of dosing (GD 6 and GD7). There was also an increase in excessive salivation in the 300 mg/kg/day group. However, since there was no other

evidence of treatment-related toxicity, the finding at 300 mg/kg/day is not considered toxicologically significant. Body weight was significantly decreased from GD9-20, however, since the body weight decreases ranged from 4-6%, these were not considered to be adverse since they were <10%. Although body weight gain was significantly decreased in the 1000 mg/kg/day group during GD 6-16 (83% of control value; $p<0.05$), GD 6-20 (88% of control value; $p<0.05$) and GD 0-20 (88% of control value; $p<0.01$), the body weight gain was not considered to be adverse since there was no effect on body weight. Although food consumption was significantly decreased (6-15%) at various intervals during dosing, it was not considered to be adverse since body weight was not adversely decreased.

The maternal LOAEL is 1000 mg/kg bw/day based on increased incidence of death and clinical signs of toxicity (clonic and/or toxic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation). The maternal NOAEL is 300 mg/kg bw/day.

In the 1000 mg/kg/day group, there was a slightly decreased number of implantations per dam (14.6± 1.7 (7.6%↓) vs 15.8±2.6 in controls), decreased live fetuses/dam (13.8±2.1 (9%↓) vs 15.2±2.6 in controls) and increased number of early resorptions/dam (0.8±0.8 (60% increase) vs 0.5±1.0 in controls). There's a slight decrease in the number of corpora lutea/dam which is reflected in the number implantations/dam. Implantations occur prior to dosing, and, therefore, are not considered to be an adverse, treatment-related effect. The decreased number of fetuses/dam is a reflection of the decreased corpora lutea and subsequent decrease in implantations. In addition, resorptions/dam values had standard deviations that were equal to or greater than the mean. The resorptions/dam at 1000 mg/kg/day of 0.6±0.6 was also within the historical control range of the testing laboratory. The historical control average (range) for early resorptions at the test facility was 0.7 (0.5-1.0). Therefore, the early resorption were not considered to be adverse. There was also a statistically significant decrease ($p<0.05$; 96% of control value) in mean fetal body weight, however, since the decrease was <5% if was not considered to be adverse. No significant developmental anomalies or malformations were noted.

The developmental NOAEL = 1000 mg/kg/day, the highest dose tested. The developmental LOAEL is not established.

The developmental toxicity study in the rat is classified Acceptable/Guideline and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental (teratology) study (MRID# 43928925), rats (Strain: Tif: RAI f (SPF), hybrids of RII/1 x RII/2 from Animal Production, WST-455, CIBA-GEIGY Limited, 4332 Stein, Switzerland) received either 0, 5, 50, 500, or 1000 mg/kg/day S-metolachlor (CGA-77102 Technical) (Batch No.: v. 4673/7 with a purity of 95.6%) suspension in 0.5% (w/w) aqueous solution of sodium carboxymethylcellulose by oral gavage from gestation days 6 through 15. No treatment related mortality was noted. There was a dose related increase in clinical signs (exhibited as pushing head through bedding for about one hour) seen at all 500 and 1000 mg/kg/day animals and 9/24 of the 50 mg/kg/day animals. This was noted throughout the dosing

period (GD 6-15). This effect was considered to be treatment related, but not adverse, since the significance of this effect is unclear and no other clinical signs were noted. The 500 and 1000 mg/kg/day dose groups had significantly lower overall body weights at gestation days 15 and 21. The body weight decreases, while statistically significant, were not considered to be adverse since the decrease was <10%. The 500 and 1000 mg/kg/day groups also gained less weight than the control during the dosing period gestation days 6-16 and for the calculated periods of gestation days 6-21 and 0-21, also for corrected body weight gains from gestation days 6-21. While the body weight gains were statistically significant, they were not considered to be adverse since there was no adverse effect on body weight. The 500 and 1000 mg/kg/day dose groups also had reduced food consumption during the dosing period (gestation days 6-16, statistically significantly different), reduced food consumption following the dosing period and for the overall periods (gestation days 6-21 and 0-21). This is also reflected in reduced food efficiency for the same periods (6-16, 6-21, 6-21, and 0-21). The decreased food consumption and food efficiency was not considered to be adverse since there was no adverse effect on body weight.

The maternal toxicity NOAEL was 1000 mg/kg/day, the highest dose tested. The maternal LOAEL was not achieved.

No significant treatment related developmental toxicity was noted at the dose levels tests. The developmental toxicity NOAEL was 1000 mg/kg/day, the highest dose tested. The developmental LOAEL was not achieved.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements (§ 83-3a) for a teratology study in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a prenatal developmental toxicity study (MRID 00041283), CGA-24705 (metolachlor) (95.4% a.i.) in 0.75% aqueous hydroxy methylcellulose was administered by gavage (10 ml/kg) to 16 pregnant New Zealand White rabbits/group from gestation days (GD) 6 through 18, inclusive, at dose levels of 0, 36, 120 or 360 mg/kg/day. The animals were sacrificed on GD 30 and the fetuses examined for evidence of developmental effects.

One doe at 36 mg/kg/day and another at 360 mg/kg/day died on GDs 24 and 29, respectively. The cause of death in both animals was considered spontaneous and possibly attributed to persistent anorexia. Anorexia was defined as less than ½ of the daily food allotment eaten; however, no food consumption data were provided to support this. The deaths were not attributed to the test material. Two rabbits aborted, one at 120 mg/kg/day (GD 25) and another at 360 mg/kg/day (GD 17). The high-dose animal had persistent anorexia. The abortions were considered to be spontaneous. Body weight decreases at all doses were <10% throughout the dosing period GD 6-18 until the end of the study. Since the body weight decreases were <10%, this effect was not considered to be adverse. In addition, the description of anorexia (i.e. decreased food consumption) which was seen at all doses, was not considered treatment-related or adverse due to no effects on body weight as well as no food consumption data provided. There was no treatment-related increase in gross pathological findings in maternal animals at necropsy.

No treatment-related increase in external, visceral or skeletal developmental effects was observed.

The maternal LOAEL was not established. The maternal toxicity NOAEL was 360 mg/kg/day (highest dose tested).

The developmental toxicity LOAEL was not established. The developmental toxicity NOAEL was 360 mg/kg/day.

The study is classified as Acceptable/Guideline and satisfies the guideline requirements for a prenatal developmental toxicity study in rabbits (83-3b; OPPTS 870.3700).

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental (teratology) study (MRID 43928924), sexually mature virgin female New Zealand White, S.P.F. Rabbits (Strain: Har:PF/CF(NZW)BR) from H.A.R.E., Rabbits for Research, Hewitt, N.J. Received either 0, 20, 100, or 500 mg/kg/day S-metolachlor (CGA-77102 Technical) (Lot No. FL-830813 with a purity of 89.6% (93.7% S isomer) suspension in 3% corn starch containing 0.5% Tween 80 by oral gavage from gestation days 7 through 19.
No treatment related mortality was noted. There was a dose related increase in little/none/soft stool observations at the 100 and 500 mg/kg/day dose levels. The 500 mg/kg/day dose group had lower overall body weights at gestation days 19, 29 and corrected body weights at day 29 gained less weight than the control during the dosing period (gestation days 7-19) with a rebound weight gain following the dosing period (gestation days 19-29), an indicator of toxicity. This group also had lower overall weight gain for the calculated periods of gestation days 7-29, 0-29 and corrected body weight gains for 0-29. This was supported by reduced food consumption during the dosing period (gestation days 7-19) and for the overall periods (gestation days 7-28 and 0-28) with a rebound in food consumption following dosing (gestation days 19-28) at the 500 mg/kg/day dose level. This is also reflected in reduced food efficiency for the same periods (719, 7-28, and 0-28) and increased food efficiency following dosing (19-28) at the 500 mg/kg/day dose level. The maternal toxicity NOAEL was 20 mg/kg/day with a LOAEL of 100 mg/kg/day based on clinical signs of toxicity.

No significant treatment related developmental toxicity was noted at the dose levels tests. The developmental toxicity was equal to or greater than 500 mg/kg/day, a LOAEL was not reached.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements [870.3700 (§83-3b)] for a teratology study in rabbits.

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

In a two-generation reproduction study (MRID 00080897), metolachlor (95.4% a.i.) was administered in the diet to two consecutive generations of 15 male/30 female CD albino rats at dose levels of 0, 30, 300 or 1000 ppm (F_0 males: 0, 2.4, 23.5 and 75.8 mg/kg/day; F_0 females: 0, 2.5, 26.0 and 85.7 mg/kg/day; F_1males: 0, 2.3, 23.7 and 76.6 mg/kg/day; F_1 females: 0, 2.6, 25.7 and 84.5 mg/kg/day).

There were no deaths in the F_0 generation. Two females of the F_1 generation died during the pre-mating period, one in the 300 ppm group at 32 days and the other in the 1000 ppm group at 52 days. One female in the 300 ppm group was found dead on gestation day 19 and a control group female was sacrificed in a moribund condition on lactation day 1. Based on necropsy examinations, none of the deaths was treatment-related. There were no treatment-related clinical signs of toxicity in either generation. Body weight, body weight gain and food consumption were unaffected in the F_0 generation. In the F_1 generation, food consumption was significantly decreased in females of the 1000 ppm group at several timepoints; however, there was no effect on body weight/body weight gain. Therefore, this finding was not considered toxicologically significant. There were no treatment-related effects on organ weights or gross/microscopic necropsy examinations in either generation.

There was no evidence of a treatment-related effect on any of the reproductive parameters for either generation. At 300 ppm, offspring body weight in females was decreased by 5% compared to control in the F_1 litter (not statistically significant) and in the F2 litter (statistically significant) at LD21. The decreased pup weight at 300 ppm was not considered to be treatment related and adverse since the effect occurred in only one sex and one timepoint (PD21). At 1000 ppm offspring body weight was significantly decreased in both sexes in the F1 litter on lactation days 14 and 21 (↓4-9% compared to control value) and in the F_2 litter on lactation days 4, 7, 14 and 21 (↓5-8% compared control value). It was a robust endpoint with decreased pup weight of >5% occurring in both sexes, at multiple time points (LDs 4, 7, 14, 21), with statistical significance at all timepoints. Therefore, the decreased pup weight in both sexes at 1000 ppm was considered to be treatment related and adverse in F_1 and F_2 litters.

The parental toxicity LOAEL was not established. The NOAEL was 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day).

The reproductive toxicity LOAEL was not established. The NOAEL was 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day).

The offspring LOAEL was 1000 ppm (F_0 males: 75.8 mg/kg/day/F_0 females: 85.7 mg/kg/day) based on decreased pup body weight in both sexes in F_1 and F_2 litters. The NOAEL is 300 ppm (F_0 males: 23.5 mg/kg/day/F_0 females: 26.0 mg/kg/day).

The study is classified as Acceptable/Guideline and satisfies the guideline requirements for a multi-generation reproduction study in rats (83-4; OPPTS 870.3800).

A.4.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

See 870.4300a.

870.4100b Chronic Toxicity - Dog

In a chronic toxicity study (MRIDs 40980701, 41164501, 42218601 and 42218602), metolachlor (97% a.i.) was administered in the diet to Beagle dogs (6/sex/group for control and high dose groups; 4/sex/group for low- and mid-dose groups) at dose levels of 0, 100, 300 or 1000 ppm (males: 0, 3.5, 9.7 and 32.7 mg/kg/day, respectively; females: 0, 3.6, 9.7 and 33.0 mg/kg/day, respectively) for one year. Two dogs of each sex in the control and high-dose group designated as recovery animals were treated for 52 weeks and were then allowed a 4-week recovery period. An additional 4 dogs/sex/group were treated at the same dose levels and sacrificed at 13 weeks.

There were no treatment-related deaths or clinical signs of toxicity. Mean body weight decreases in the 1000 ppm group were <10% throughout the 52-week study and were not considered to be adverse. Mean body weight gain was decreased in the 1000 ppm group females, considering both all animals (5-17% decrease) and only those treated for 52 weeks (5-17% decrease), however these were not considered to be adverse since there was no adverse effect on body weights. Alkaline phosphatase was significantly increased in the 1000 ppm females at weeks 12, 26 and 40; however, the increase was not considered toxicologically significant due to the small magnitude of the effect (39-45% increase), no other clinical chemistry findings, and the lack of accompanying necropsy findings.

The LOAEL for males and females was not established. The NOAEL for males and females was 1000 ppm (32.7/33.0 mg/kg/day) (highest dose tested).

The study is classified as Acceptable/Guideline and satisfies the guideline requirements for a chronic toxicity study in dogs (83-1; OPPTS 870.4100.

A.4.5 Carcinogenicity

870.4200a Carcinogenicity Study - rat

In a combined chronic toxicity/carcinogenicity study (MRID 00129377), groups of 60 CD [CD-Crl:CD(SD)BR] rats/sex/dose were administered metolachlor (95.3% a.i.; batch # FL-800362) in the diet at dose levels of 0, 30, 300, or 3000 mg/kg (equivalent to 0, 1.5, 15, and 150 mg/kg bw/day) for up to 24 months. Additional groups of 10 rats/sex/dose were administered metolachlor in the diet at 0 or 3000 mg/kg for 12 months; 5 rats/sex/dose were euthanized immediately after cessation of treatment, and the remaining 5 rats/sex/dose were allowed to recover for four weeks.

There were no adverse effects of treatment observed on mortality, clinical signs, hematology, clinical chemistry, urinalysis, or gross pathology. In the 3000 mg/kg females, body weights were

decreased by 5-10% during Weeks 6-78, and continued to be decreased by 10% at Week 104, resulting in an overall (Weeks 0-104) decrease of 13% in body weight gains. The decreased body weights were accompanied by generally decreased food consumption throughout treatment. Additionally, at 3000 mg/kg, terminal body weights were decreased by 6%, and increases were noted in the absolute (↑7%), relative to body (↑13%), and relative to brain (↑5%) liver weights of the in the main study males. Terminal body weights were decreased by 19%, and increases were observed in absolute liver weights when subjected to an analysis of covariance with terminal body weight as the covariate (↑24%) and in relative to body liver weights (↑25%) of the males euthanized after 12 months of treatment. Additionally, in the males allowed to recover for 4 weeks following 12 months of treatment, increases were seen in the absolute (↑14%), relative to body (↑9%), and relative to brain (↑17%) liver weights. The total incidence of foci of cellular alteration of the liver, including eosinophilic, clear, and basophilic foci, was increased in both the males (35/60 treated vs. 21/59 control) and females (46/60 treated vs. 15/60 control), and the total number of rats with these findings were increased in both males (29/60 treated vs. 19/59 control) and females (34/60 vs. 13/60 control).

The LOAEL for systemic toxicity is 3000 mg/kg (150 mg/kg/day), based on decreased body weights and food consumption in the females, and increased absolute, relative to body, and relative to brain liver weights in males, and non-neoplastic microscopic findings of foci of cellular alteration in the liver of the males and females. The NOAEL is 300 mg/kg (equivalent to 15 mg/kg/day).

This study is Acceptable/Guideline and satisfies the guideline requirement for a chronic toxicity/carcinogenicity study OPPTS 870.4300); OECD 453] in the rat. This study was performed prior to the adoption of the Pesticide Assessment Guidelines, Subdivision F, October 1982 (revised November, 1984).

Treatment-related increases in liver tumors were seen at 3000 ppm in female rats. No treatment-related tumors were seen in male rats. Dosing was considered adequate based on decreased body weights and food consumption noted in the females, increased liver weights in males, and non-neoplastic microscopic findings in the liver (foci of cellular alteration) of the males and females.

870.4200b Carcinogenicity (feeding) - Mouse

In a carcinogenicity study (MRID 00117597), metolachlor (reported to be 95% a.i.) was administered in the diet to 68 CD-1 mice/sex/group at doses of 0, 300, 1000 or 3000 ppm (0, 45, 150 or 450 mg/kg/day, based on 1ppm equals 0.150 mg/kg/day). Eight mice/sex/group were sacrificed at 12 and 18 months.

High dose females had a significant increased mortality rate due to a number of deaths during the first few weeks of treatment (control: 24/52; high dose females: 34/52 at termination) . Although the deaths were possibly attributable to a viral infection, the contribution of the test material can't be dismissed. Body weight was statistically significantly decreased (91-95% of control value) throughout the study in the 3000 ppm males and during the latter half of the study in the 3000 ppm females (93-95%). Body weight gain was consistently decreased in the 3000 ppm males (48-88%) and females (59-86%). Food consumption was comparable between treated and

control groups until week 90 of treatment, at which time the 3000 ppm males consumed 10% less than controls. The decrease was statistically significant at weeks 98, 102 and 104. There was no significant effect on female food consumption. There was no evidence of a treatment-related effect on hematology or clinical chemistry parameters. Organ weight was not affected except for a dose-related decrease in the absolute and relative weight of the seminal vesicles of males which was statistically significant at the high dose. However, there was no effect on testes weight and no accompanying histological changes in the seminal vesicles; therefore, the toxicological significance of the finding is questionable. There were no treatment-related microscopic changes. There was no treatment-related increase in tumor incidence in the study.

The LOAEL was 3000 ppm (450 mg/kg/day) based on possible treatment-related deaths in females and decreased body weight/body weight gain in males and females. The NOAEL was 1000 ppm (150 mg/kg/day).

The HED Cancer Peer Review Committee evaluated the carcinogenic potential of metolachlor on several occasions. At the 4th Committee meeting on July 27, 1994, it was metolachlor was classified as a Group C, possible human carcinogen based on liver tumors in the rat with risk quantitated using a Margin of Exposure approach.

The study is classified as Acceptable/Guideline and satisfies the guideline requirements for a carcinogenicity toxicity study in mice (83-5; OPPTS 870.4200).

A.4.6 Mutagenicity

Mutagenicity studies with metolachlor and S-metolachlor are listed in Appendix A, Table A.2.2.

The tables below show there was no evidence of mutagenicity *in vitro* or *in vivo* with either CGA 354743 or CGA 51202, both of which are metolachlor metabolites.

Table A.4.6.1. Mutagenicity Studies with CGA 354743 (ethane sulfonate degradate of metolachlor [Metolachlor ESA])

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Gene Mutation 870.5100 *Salmonella/Escherichia* bacterial reverse mutation assay	44931712 (1996) acceptable/guideline 312.5, 625.0, 1250.0, 2500.0 and 5000.0 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix) TXR No. 0050330	Strains TA98, TA100, TA102, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to CGA-354743 tech. in DMSO at concentrations of 312.5-5000.0 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix). There was no evidence of induced mutant colonies over background.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Gene Mutation 870.5300 mammalian cell gene mutation assay at the HPRT locus, Chinese hamster V79 cells	44991102 (1999) acceptable/guideline concentrations of 185.19, 555.56, 1666.67, 5000.00 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix). TXR No. 0050330	Chinese hamster V79 cells in culture were exposed to CGA-354743 tech. in distilled water at concentrations of 185.19 - 5000.00 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix). There was suggestive (statistical) evidence of a possible induction of mutant colonies over background; however, the results are unlikely to be biologically significant because the absolute numbers of mutant colonies were low and within the testing laboratory's historical solvent control ranges.
Cytogenetics 870.5395 Micronucleus assay in mouse bone marrow cells	44931713 (1998) acceptable/guideline 1250, 2500 and 5000 mg/kg body weight TXR No. 0050330	Five mice/sex/dose were treated once each via oral gavage with CGA-354743 tech. at doses of 1250 - 5000 mg/kg body weight. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any dose or treatment time.
Other Effects 870.5503, Unscheduled DNA Synthesis	44931714 (1998) acceptable/guideline concentrations of 9.77, 39.06, 156.25, 625.00, 2500.00, 5000.00 µg/mL TXR No. 0050330	Primary rat hepatocyte cultures were exposed to CGA-354743 tech in distilled water at concentrations of 9.77 - 5000.00 µg/mL for 16 to 18 hours in an initial assay and to concentrations of 78.13 - 2500 µg/mL for 16 to 18 hours in a confirmatory assay. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.

Table A.4.6.2. Mutagenicity Studies with CGA 51202 (Metolachlor oxanilic acid [Metolachlor OA])

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Gene Mutation 870.5100 *Salmonella/Escherichia* bacterial reverse mutation assay	44929512 (1992) acceptable/guideline 312.5, 625, 1250, 2500, 5000 ug/plate TXR No. 0050330	Strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to CGA-51202 technical in DMSO at concentrations of 312.5 - 5000.0 µg/plate in the presence and absence of mammalian metabolic activation. There was no evidence of induced mutant colonies over background.
Cytogenetics 870.5395, Micronucleus assay in mouse bone marrow cells	MRID 44929511 (1992) 600, 1200 or 2400 mg/kg Acceptable/Guideline TXR No. 0050330	Five mice/sex/dose were treated once via oral gavage with CGA-51202 technical at doses of 600-2400 mg/kg body weight. There was no biologically significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any dose or treatment time used in the study.
Gene Mutation 870.5300 mammalian cell gene mutation assay at the HPRT locus, Chinese hamster V79 cells	MRID 45001201 (1999) 500, 1000, 2000 or 4000 ug/mL in initial assay; 375, 750, 1500 or 3000 ug/mL in confirmatory assay, in the presence and absence of mammalian metabolic activation (S9-mix). TXR No. 0050330	CGA 51202 tech. was tested up to cytotoxic concentrations. Statistically significant increases in mean mutant frequency were seen in the initial assay with S9-mix at 500 µg/mL (6.66 x 10^6) and 1000 µg/mL (5.56 x 10^6) compared to the solvent control value of 4.02 x 10^6 and without S9-mix at 500 µg/mL (15.35 x 10^6) compared to the solvent control value of 12.90 x 10^6. The increases were small and the actual mean mutant frequencies were within the range of historical solvent control values. No positive dose-response was seen and no statistically significant increases in mean mutant frequencies were seen in the confirmatory assay. The solvent and positive controls induced the appropriate response. There was no evidence of a biologically significant induction of mutant colonies over background.

A.4.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

Recommended for a waiver by HASPOC (Van Alstine, J., 03/20/2013, TXR 0056586).

870.6200 Subchronic Neurotoxicity Screening Battery

Recommended for a waiver by HASPOC (Van Alstine, J., 03/20/2013, TXR 0056586).

870.6300 Developmental Neurotoxicity Study

Recommended for a waiver by HASPOC (Van Alstine, J., 03/20/2013, TXR 0056586).

A.4.8 Metabolism

870.7485 Metabolism - Rat

[Phenyl-U-^{14}C] labeled CGA-77102 (S-metolachlor) was administered by gavage to groups of Tif: RAI f (SPF) strain rats at a single low dose (0.5 mg/kg, Group B1), at a high dose (100 mg/kg, Group D1), or at a low dose following 14-daily oral high doses with the unlabeled test chemical (Group V1) (MRID 44491401). The urine and feces were collected at specified times (from 5 animals/sex) to determine the extent of absorption and excretion; selected tissues were harvested after seven days. Blood samples from Groups B1 and D1 were taken periodically to determine the kinetics in plasma and blood cell (RBC); the expired air in Group D1 was also monitored for $^{14}CO_2$ for 72 hours. In a bile cannulation study in male rats (6/group), bile and excreta were collected at defined intervals up to 48 hours after the labeled test substance was administered at a single oral low (Group G1) or high (Group G2) dose. In all three dose groups (B1, D1, and V1), the seven day combined levels of radioactivity in urine were 31.1 - 36.5% for males and 40.8 - 45.5% for females; the fecal levels were 60.2 - 62.5% for males and 48.9 - 55.0% for females. Only 0.1% or less was eliminated in the expired air. The total recovery ranged from 96.5 ± 2.3% to 99.3 ± 0.9% which indicates an excellent efficiency of the study. The route or extent of excretion was slightly influenced by the sex of the animal but not by pretreatment with non-radiolabeled CGA-77102 or by the dose level. The degree of absorption, based on adding the cumulative urinary excretion to the total residues in tissues, was 35 - 39% in males and 43 - 49% in females of both dose groups. However, based on the bile duct cannulation study, most of CGA-77102 was absorbed from the gastrointestinal tract since 85% of the dose was recovered in urine, bile fluid, and tissues during the 48 hours study period. Therefore, the biliary excretion and enterohepatic circulation play a significant role in the elimination process of CGA-77102.

Irrespective of the dose and sex, there seems to be a biphasic plasma profile with two concentration maxima (C_{max}); a fast rising first C_{max} was reached at 0.25 - 1 hour post dosing which was succeeded by a second C_{max} at 8 and at 12 - 24 hours following administration of the low and high dose, respectively. In the low dose group (B1), the first and second C_{max} were nearly identical (~ 0.03 µg/ml); in the high dose group (D1), the first and second C_{max} were, respectively, 4.6 and >3.9 µg/ml in males and 2.2 and 4.5 µg/ml in females. The time to half maximum plasma concentration ($t_{cmax/2}$) in males/females was 31/24 hours at the low dose and 44/32 hours at the high dose. Bioavailability, or the area under the plasma concentration curve ($AUC_{0\text{-}48hr}$), was nearly identical (~ 0.8 mg/kg.hr) among males and females of the low dose group. Also, both sexes in the high dose group had similar plasma $AUC_{0\text{-}48hr}$ (M/F: 143/125 mg/kg.hr) which increased almost proportionately with the 200-fold increase in the dose level. The residues in RBC increased steadily with time reaching peak levels (at 24 - 48 hours post-dosing) of 0.5-0.6 and 90 ppm (or µg/g) CGA-77102 equivalents for the low (B1) and high (D1) dose groups, respectively. The peak levels in RBC remained high and were nearly 20 fold higher than the respective plasma C_{max} levels.

The kinetics of tissue distribution and depletion in both sexes were also followed for up to 144 hours following a single low or high oral dose (Groups F1 - F4). Peak residue levels were reached within 12 - 24 hours and ranged from 0.007 ppm (female muscle) to 0.123 ppm (male kidneys) at the low dose, and from 1.29 ppm (male brain) to 16.82 ppm (male liver) at the high dose, with the highest levels being among some of the well-perfused tissues (e.g., liver, kidneys, spleen, and lungs). The extent of residue depletion was variable among the tissue types but was minimally affected by the dose or the sex of the animal. The radiolabel was most persistent in some of the well-perfused organs (e.g., the heart, lungs, and spleen) in addition to the brain and bone where, after 144 hours, the levels were decreased to only 45 - 94% of their maximal concentrations. In Groups F1 - F4, peak residue concentration in the whole blood (0.2 and 42 - 47 µg/ml in the low and high dose groups, respectively) was reached at 24 hours and was maintained throughout the study. Overall, the high/low dose peak tissue levels (including blood) ranged from 132 to 282 which approximates the 200-fold increase in dosage.

Finally, it should be reemphasized that CGA-77102 has a high affinity for and a long half-life in blood (especially RBC) which might contribute to the retarded depletion of tissue residues.

This study is classified as Acceptable/Guideline and satisfies the requirement for a series 85-1 general metabolism study for S-metolachlor (CGA-77102).

870.7485 Metabolism - Rat

In a rat metabolism study (MRID 43164201),14C-Metolachlor was administered orally in PEG-200 [HWI 6117-208] or corn oil [ABR-94001] to groups (5 sex/dose) of male and female Sprague-Dawley rats at a low oral dose (1.5 mg/kg), repeated low oral dose (1.5 mg/kg x 14 days), and a single high dose (300 mg/kg). Control animals (1/sex) received blank formulation. Comparison of oral and intravenous data showed that of the administered dose, between 69.6% and 93.2% was absorbed. Distribution data showed that the only significant sites of residual radioactivity at 7 days post-dose were residual carcass (0.9 - 2.2% of the administered dose) and red blood cells (0.95- 1.53 µg equivalents/gram in blood cells for all low dose male and female rats). Dosing regimen did not result in any apparent accumulation of residual radioactivity. Excretion data showed that urine and feces were both significant routes for elimination of metolachlor derived radioactivity. In the low dose groups, the urine appeared more of a predominant route for excretion in female rats than in males, whereas fecal excretion was slightly higher in males. However, at the high oral dose, there were no apparent sex-related differences in the pattern of urinary excretion. Examination of urinary excretion data as presented in graphical format indicated that at the 300 mg/kg dose, excretion was delayed vs the low oral dose, suggesting saturation of elimination.

Metabolism of metolachlor in this study was complex, with up to 32 metabolites identified in urine and/or feces. The "major" urinary metabolite found in all dose groups was the metabolite designated CGA-46129. This metabolite was present as 5.6-13.1% of the total radioactive residue (TRR) in rat urine across all dose groups, and was highest in the intravenously dosed group. In the orally dosed rats, the percentage of this metabolite decreased from approximately 13% of TRR co between 5.6-9.2% of TRR. Other metabolites identified in urine which constituted near or at 5% of TRR were UlO (CGA- 37735), Ul3, Ul7, Ul, •polar 1", and •polar

2." The radioactivity constituting the 'polar 1' and 'polar 2' regions was further broken down to at least 12 components by TLC, but the identity of the metabolites in these regions was not demonstrated.

In feces, a similarly complex metabolite profile was obtained. The •major" metabolite observed in feces, F9, was identical to U7, or CGA-46129. Except for intravenously dosed rats, where the percentage of this metabolite in feces was equivalent in male and female rats (11.6 and 13.2% of TRR, respectively), the percentage of F9 in feces of orally dosed rats was always higher in males than in females. Other fecal metabolites identified at or near 5% of TRR in feces included F2 (CGA-41638), F3 (CGA-133275), F7, F8 and F8', F16, F14, and F17.

Based on these data, a scheme for metabolism of metolachlor was proposed.

This metabolism study in rats is Acceptable/Guideline and satisfies the requirements for a Metabolism and Pharmacokinetics study [OPPTS 870.7485 (§85-1)].

A.4.9 Dermal Absorption Rat

In a dermal penetration study (MRID 41833102), 14C-CGA 24 705 (% a.i. unknown) suspended in deionized water was applied to a 10 cm2 area of the backs of 4 male Crl:CD®BR rats/group at doses of 0.01, 0.1 or 1.0 mg/cm2 • Each dose group was exposed for either 2, 4, 10 or 24 hours and then the area was washed and the animals sacrificed. Another 4 animals/dose group were treated for either 1O or 24 hours, the skin was washed and they were placed in a metabolism cage for collection of urine and feces. Sacrifice was 72 hours later. The amount of radioactivity in the blood, urine, feces, carcass, skin and cage wash was determined for all animals.
CGA 24705 was rapidly absorbed with significant bioaccumulation. The total percentage of the applied dose which was found in the blood, urine, feces, carcass and cage wash (or absorbed) after 10 hours was 32.93, 20.26 and 6.98 at 0.01, 0.1 and 1.0 mg/cm2, respectively. The percentage remaining on the skin was 24.66, 20.89 and 12.69 at the respective doses. The total percentage of the applied dose in the blood, urine, feces, carcass and cage wash (or absorbed) after 24 hours was 62.84, 26.85 and 16.15 at 0.01, 0.1 and 1.0 mg/cm', respectively. The percentage remaining on the skin was 11.09, 19.14 and 15.49 at the respective doses.
For rats with skin washings at 10 hours and sacrifice 72 hours after washing, the total percentage of the applied dose found in the blood, urine, feces, carcass and cage wash was 50, 38.61 and 15.46 at 0.01, 0.1 and 1.0 mg/cm2, respectively. The percentage remaining on the skin was 5.30, 3.48 and 3.54 at the respective doses. For rats with skin washings at 24 hours and sacrifice 72 hours after washing, the percentage of the applied dose found in the blood, urine, feces, carcass and cage wash was 67 .32, 43.46 and 30.49 at 0.01, 0.1 and 1.0 mg/cm2, respectively. The percentage remaining on the skin was 3.39, 1.36 and 1.42 at the respective doses.

The study is classified as Acceptable/guideline and satisfies the guideline requirements for a dermal penetration study in rats (85-3; OPPTS 870.7600).

A.4.10 Immunotoxicity

870.7800 Immunotoxicity

In an immunotoxicity study (MRID 48783301), S-metolachlor (98.6% a.i., Lot # CAB9J054) was administered in the diet for 28 consecutive days (Days 0-27) to female Crl:CD-1 (ICR) mice (10 animals/dose) at doses of 0, 1500, 3000 or 5000 ppm (0, 304.3, 639.5 or 1108.5 mg/kg/day, respectively). Four days prior to sacrifice, animals in all groups were immunized with a suspension of sheep red blood cells (SRBC) by intravenous injection (1 x 108 SRBC/animal, 0.2 mL/animal dose volume). Animals in the positive control group received intraperitoneal injections of cyclophosphamide (50 mg/kg bw/day) on Days 24-27. All animals were evaluated for mortality, clinical signs, body weight changes, and gross pathology. On Day 28, animals were sacrificed and spleens were collected. Spleen cell suspensions were prepared, spleen cell counts were performed, and the numbers of specific IgM antibody-forming cells directed towards the SRBC antigen were determined to measure the humoral immune response using the splenic Antibody-Forming Cell (AFC) assay.

There were no treatment-related effects on clinical observations, body weight, body weight gain, food consumption, and spleen or thymus weights. A higher liver weight (absolute and adjusted) was noted at all dosage levels of S-metolachlor, with significant differences noted in the mid and high doses.

The NOAEL for systemic toxicity in female mice is 5000 ppm (actual dose of 1108.5 mg/kg/ bw/day); the LOAEL was not established.

For immunotoxicity, there were no statistically significant treatment-related effects on anti-SRBC AFC response. A high inter-individual variability was noted in all the treatment groups as well as in the control group. Examination of individual animal data did not show any trend or distribution that would demonstrate significant suppression of the anti-SRBC AFC response. The positive control group showed a statistically significant reduction in the anti-SRBC AFC response, confirming the validity of the immunotoxicity assay.

A natural killer (NK) cell activity assay was not performed. The toxicology database for S-metolachlor does not reveal any evidence of treatment-related effects on the immune system. The overall weight of evidence suggests that this chemical does not directly target the immune system. Under HED guidance, a NK cell activity assay is not required at this time.

Under the conditions of this study, the NOAEL for immunotoxicity in female mice is 5000 ppm (actual dose of 1108.5 mg/kg/ bw/day). The LOAEL for immunotoxicity was not determined.

This immunotoxicity study is classified Acceptable/Guideline and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in the mice.

A.4.11 Other – Mode of Action Studies

Non-guideline studies

1. In a non-guideline, enzyme and DNA synthesis induction study in cultured female human hepatocytes (MRID 49927702), primary female human hepatocyte cultures were exposed to S-metolachlor (98.8% a.i., Batch # CAB2H12058) in 0.5% (v/v) DMSO at concentrations of 0, 1, 5, 10, 20, 40, or 75 µM for 96 h. Cytotoxicity was determined by measurement of intracellular adenosine-5'-triphosphate (ATP) levels; induction of DNA synthesis was determined by measurement of nuclear incorporation of 5-bromo-2-deoxyuridine (BrdU); and enzyme induction was determined by measurement of pentoxyresorufin-*O*-dependentylation (PROD) and benzyloxyresorufin-*O*-debenzylation (BROD) activities. Hepatocyte cultures were also exposed to phenobarbital sodium (PB) at 10, 100, or 1000 µM as a positive control for enzyme induction, and to epidermal growth factor (EGF) at 25 ng/mL as a positive control for induction of replicative DNA synthesis.

S-metolachlor treatment resulted in cytotoxicity at 40 and 75 µM, but did not induce DNA synthesis or enzyme activity at any concentration tested under the conditions of this study. The cultured female human hepatocytes responded as expected to the positive controls for DNA synthesis (EGF) and enzyme induction (PB).

This study is classified as Acceptable/Non-guideline and satisfies the intended purpose of examining enzyme and DNA synthesis induction in cultured female human hepatocytes.

2. In a non-guideline, enzyme and DNA synthesis induction study in cultured female Sprague Dawley rat [Crl:CD(SD)] hepatocytes (MRID 49927704), primary female rat hepatocyte cultures were exposed to S-metolachlor (98.8% a.i., Batch # CAB2H12058) in 0.5% (v/v) DMSO at concentrations of 0, 1, 5, 10, 20, 40, or 75 µM for 96 h. Cytotoxicity was determined by measurement of intracellular adenosine-5'-triphosphate (ATP) levels; induction of DNA synthesis was determined by measurement of nuclear incorporation of 5-bromo-2-deoxyuridine (BrdU); and enzyme induction was determined by measurement of pentoxyresorufin-*O*-dependentylation (PROD) and benzyloxyresorufin-*O*-debenzylation (BROD) activities. Hepatocyte cultures were also exposed to phenobarbital sodium (PB) at 10, 100, or 1000 µM as a positive control for enzyme induction, and to epidermal growth factor (EGF) at 25 ng/mL as a positive control for induction of replicative DNA synthesis.

S-metolachlor treatment decreased intracellular ATP levels in the 75 µM group, indicating cytotoxicity at this concentration. Treatment with S-metolachlor at ≥1 µM caused consistent increases in the BrdU labeling index indicating induction of DNA synthesis, although strict dose-dependency was not observed. Treatment with PB at ≥10 µM resulted in increases in a dose-dependent manner. Treatment with 25 ng/mL EGF caused an increase in the BrdU labeling index, indicating the hepatocytes responded as expected to the positive control. There were no effects of S-metolachlor treatment on PROD activity. Treatment with 100 and 1000 µM PB caused increases in PROD activity, indicating the hepatocytes responded as expected to the positive control. Treatment with S-metolachlor at ≥10 µM caused increases in BROD activity indicating induction of CYP 2B/3A, although strict dose-dependency was not observed.

Treatment with 100 and 1000 µM PB caused increases in BROD activity, indicating the hepatocytes responded as expected to the positive control.

This study is classified as Acceptable/Non-guideline and satisfies the intended purpose of examining enzyme and DNA synthesis induction in cultured female rat hepatocytes.

3. In a non-guideline, oral mechanistic study (MRID 49927706), S-metolachlor (98.8% a.i.; Batch # CAB2H12058) was administered to 50 Sprague Dawley [Crl:CD(SD)] female rats/dose in the diet at dose levels of 0, 300, 3000, or 5000 ppm (equivalent to 0, 32.2, 303.1, and 536.4 mg/kg/day) for up to 14 days. An additional group of 20 female Sprague Dawley rats was administered sodium phenobarbital (PB) in the diet at 1200 ppm (equivalent to 122.4 mg/kg/day) for up to 8 days as positive controls. Ten rats/sex/dose were euthanized on Days 2, 3, 4, 8, and 15. Hepatocellular proliferation was measured by incorporation of 5-bromo-2'deoxyuridine (BrdU), and induction of hepatic metabolic enzymes was determined by assessing the activities of 7-pentoxyresorufin-*O*-dependentylase (PROD) and 7-benzyloxyresorufin-*O*-debenzylase (BROD). The stated objective of this study was to investigate the effects of S-metolachlor on the liver of female Sprague Dawley rats after dietary administration for up to 14 days.

No effects of treatment were observed on mortality, clinical signs, clinical chemistry, or gross or microscopic pathology.

Treatment with 300 ppm caused only minor, transient increases in PROD and BROD activities that were not considered adverse.

Body weights were decreased by 4-8% at ≥3000 ppm on Day 2; at 5000 ppm, body weights continued to be generally decreased by 5-7% during Days 3-15. Cumulative body weight losses were noted at 3000 ppm on Days 1-2 (−3.8 g treated vs. 4.7 g controls) and at 5000 ppm on Days 1-2 (−9.0 g treated vs. 4.7 g controls) and Days 1-3 (−2.7 g treated vs. 7.4 g controls). Cumulative body weight gains were decreased at 3000 ppm by 24% on Days 1-3 and by 19-73% at 5000 ppm during Days 1-15. Food consumption was decreased by 32% at 3000 ppm and by 56% at 5000 ppm for Days 1-2, and by 15% at 5000 ppm on Days 2-3. Food consumption was unaffected by treatment for the remainder of the study, suggesting the initial decreases observed were due to palatability issues. Terminal body weights were decreased at 5000 ppm by 11% on Day 4, by 8% on Day 8, and were similar to controls on Day 15. Absolute liver weights were decreased by 11% on Day 2 but were increased by 14% on Day 8 at 3000 ppm and by 17% on Day 15 at 5000 ppm. At ≥3000 ppm, adjusted liver weights were increased by 10-25% on Days 3, 4, 8 and 15. Relative to body liver weights were similar to controls for all time points and dose groups.

An increase in the BrdU labeling index (# BrdU labeled cells/1000 cells) was observed at 3000 ppm on Days 2, 3, and 4 and at 5000 ppm on Days 2 and 4. The BrdU labeling index was similar to control levels on Days 8 and 15. Hepatic microsomal protein levels were increased ($p<0.05$) by 13% at 3000 ppm on Day 15, and by 14-25% at 5000 ppm on Days 4, 8, and 15. PROD and BROD activities generally increased with dose. PROD activity was increased ($p<0.01$) as follows: 404-1159% at 3000 ppm on Days 2, 3, 4, 8, and 15; and 679-1629% at

5000 ppm on Days 2, 3, 4, 8, and 15. BROD activity was increased as follows: 457-2816% at 3000 ppm on Days 2, 3, 4, 8, and 15; and 992-2618% at 5000 ppm on Days 2, 3, 4, 8, and 15.

Treatment with the positive control (1200 ppm PB) decreased body weights by 5-8% during Days 1-8; however, cumulative body weight gains were relative unaffected by treatment. Slight decreases in food consumption were noted during Days 1-8. Terminal body weights were decreased by 10% on Day 4 and 8% on Day 8, absolute liver weights were increased by 21% on Day 8, and adjusted liver weights were increased by 23% on Day 4 and by 33% on Day 8. Minimal hepatocyte hypertrophy was observed in 4/10 rats on Day 4, becoming minimal to slight in 10/10 rats on Day 8. Minimal to slight periportal vacuolation was noted in 2/10 rats on Day 4, but not on Day 8.

Treatment with 1200 ppm PB increased the BrdU labeling index on Day 4; the labeling index was increased without significance on Day 8. Liver biochemistry showed increases in hepatic microsomal protein levels of 19-29%, PROD activity of 2744-3488%, and BROD activity of 6961-7743%, all on Days 4 and 8.

This oral mechanistic study in the rat is Acceptable/Non-guideline and satisfies the purpose for which it was intended.

4. In a non-guideline, *in vitro* study (MRID 49927707), S-metolachlor was tested for its ability to activate the constitutive androstane receptor (CAR), a xenobiotic-sensing nuclear receptor that has been found to be involved in the development of mouse liver tumors induced by exposure to phenobarbital (PB) and 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP). A luciferase reporter assay using COS-1 cells transfected with mouse, rat, or human CAR3 cDNA expression vectors, required cofactors, and a CYP2B6 response element-luciferase reporter construct was developed (Omiecinski *et al.*, 2011) and used for this study. The cells were exposed to S-metolachlor at concentrations of 1, 3, 10, or 30 µM; the previously-tested, positive, direct CAR activator, artemisinin, was used at the same concentrations; and model positive control activators CITCO, TCPOBOP, and clotrimazole for human, mouse, and rat CAR3 were incubated at appropriate single concentrations. All activations were compared to the solvent control DMSO (<0.01% v/v). Light emissions from the luciferase reporter were quantified to measure the level of CAR3 activation.

The viability assays showed the chemicals did not cause cytotoxicity, with all viabilities ≥85%.

S-metolachlor activated the CAR3 constructs in a dose-dependent manner. Human CAR3 was activated by 2.8- to 8.7-fold at concentrations ≥3 µM; mouse CAR3 was activated by 8.5- to 26.9-fold at concentrations ≥1µM; and rat CAR3 was activated by 51.3- to 57.1-fold at concentrations ≥10µM. The previously-tested, positive compound, artemisinin, activated human CAR3 by 8.2-fold at 30 µM, mouse CAR3 by 3.9- to 12.9-fold at ≥3 µM, and rat CAR3 by 37.9- to 52.4-fold at ≥10 µM. The model positive control activators CITCO, TCPOBOP, and clotrimazole activated human, mouse, and rat CAR3 by 10.3-fold, 45.3-fold, and 95.4-fold, respectively. The indirect activator phenobarbital at 1 mM did not activate human CAR3, and activated mouse and rat CAR3 by 2.1-fold and 5.9-fold, respectively.

This *in vitro*, mechanistic study in the rat is Acceptable/Non-guideline and satisfies the purpose for which it was intended.

5. In a comparative 28-day oral toxicity study (MRID 50396001), groups of eight to thirteen Tif:RAIf (SPF), Sprague Dawley-derived rats/sex/dose level/treatment were administered S-metolachlor (95.6% a.i.; Batch #V.4673/7) or metolachlor (97.7% a.i.; Batch #P.111072) in the diet at dose levels of 0, 30, 300, 3000, or 5000 ppm (S-metolachlor mean daily intake: 0, 2.65, 24.5, 242, and 426 mg/kg bw/day and 0, 2.73, 26.4, 257, 435 mg/kg bw/day for males and females, respectively; metolachlor mean daily intake[14]: 265 and 447 mg/kg bw/day for groups 4 and 5 males, respectively, and 264 and 433 mg/kg bw/day for groups 4 and 5 females, respectively) for up to four weeks. Each study group consisted of three experimental groups: (1) three rats/sex/dose evaluated for proliferating cell nuclear antigen (PCNA) on Day 7; (2) five rats/sex/dose evaluated for toxicity including laboratory investigations, PCNA assessment, electronmicroscopy, and optional biochemical investigations; and (3) five rats/sex/dose in controls and groups 4 and 5 only evaluated for reversibility after one month of recovery, including laboratory investigations, PCNA assessment, electronmicroscopy, and optional biochemical investigations. The purpose of this study was to compare the effects of treatment with metolachlor to treatment with S-metolachlor in rats. A concurrently-reviewed investigation detailed the PCNA assessment, electron microscopy, and biochemical investigation results (Persohn, 1995; MRID 50396002).

Treatment of rats with either S-metolachlor or metolachlor resulted in similar toxicological profiles. There were no treatment-related adverse effects on clinical signs, mortality, food consumption, hematology, urinalysis, and gross and microscopic examination. Additionally, animals fed metolachlor and S-metolachlor had no adverse effects on body weight.

This non-guideline 28-day study is considered supplemental information, although it was considered acceptable for regulatory purposes. This study, in conjunction with MRID 50396002, is being used to support a cancer mode-of-action for liver tumors with the intended purpose of comparing the effects of treatment with metolachlor (CGA24705) to those of S-metolachlor (CGA77102) in rats.

6. In a 28-day dietary toxicity study (Persohn, 1995; MRID 50396002), livers from a concurrently reviewed, comparative 28-day dietary toxicity study (Frankhauser, 1995; MRID 50396001) were processed for assessment of replicative liver DNA synthesis, electron microscopy, and selected hepatic biochemical parameters. In the 28-day study by Frankhauser, groups of Tif:RAIf (SPF) were administered either metolachlor (CGA24705, 97.7% a.i.; Batch # P.111072) or S-metolachlor (CGA77102, 95.6% a.i.; Batch # V.4673/7) in the diet at dose levels of 0 (13 rats/sex), 30 (8 rats/sex), 300 (8 rats/sex), 3000 (13 rats/sex), or 5000 (13 rats/sex) mg/kg for up to 28 days. The purpose of this study was to investigate the effect of metolachlor and S-metolachlor on replicative DNA synthesis in hepatocytes after dietary administration to rats for 7 and 28 days, and to determine, both biochemically and ultramorphologically, a prospective inductive effect on selected liver parameters.

[14] Mean daily intake for groups 2 and 3 could not be calculated due to technical error.

Administration of metolachlor and S-metolachlor for up to 28 days in the diet did not cause an increase in mean hepatocyte nuclear-labeling indices, protein contents of liver 100 × g supernatants or cytosolic protein levels, induction of cytosolic GST or cyanide-insensitive peroxisomal fatty acid β-oxidation activities, or induction of rat liver cytochromes CYP3A1 and CYP3A2 or CYP4A3 and CYP4A1/4A2.

A moderate proliferation of SER was observed in hepatocytes of all animals after administration of 5000 mg/kg metolachlor for 28 days. In addition, administration of 5000 mg/kg S-metolachlor for 28 days resulted in a moderate/distinct proliferation of SER in females and a moderate proliferation in males. After the 28-day recovery period, all animals that were administered 5000 mg/kg metolachlor or S-metolachlor had normal hepatocyte structural and numerical organelle characteristics.

Administration of ≥3000 mg/kg metolachlor or S-metolachlor resulted in induction of hepatic microsomal protein and cytochrome P-450 contents, as well as EROD, PROD, and UDPGT activities. Hepatic microsomal protein and cytochrome P450 contents returned to control levels in all treatment/recovery groups. In all treatment/recovery groups, EROD and PROD activities returned to control levels, except for decreased PROD activity (↓42%) in the S-metolachlor treatment/recovery females. In all treatment/recovery groups, UDPGT activities returned to control levels, except for decreased activity (↓30%) in the metolachlor treatment/recovery males.

In males administered S-metolachlor, the hepatic microsomal protein content was increased by 8-11% in the ≥3000 mg/kg groups. In males administered metolachlor, the hepatic microsomal protein content was increased by 13-25% in the ≥3000 mg/kg groups, respectively. In females administered S-metolachlor, the hepatic microsomal protein content was increased by 7-10% in the ≥3000 mg/kg groups. In females administered metolachlor, the hepatic microsomal protein content was increased by 5-12% in the ≥3000 mg/kg groups, respectively.

In males administered S-metolachlor, the microsomal cytochrome P450 content was increased by 45% and 32% in the 3000 and 5000 mg/kg groups, respectively. In males administered metolachlor, the microsomal cytochrome P450 content was increased by 35-52% in the ≥3000 mg/kg groups, respectively. In females administered S-metolachlor, the microsomal cytochrome P450 content demonstrated increases of 26-36% in the ≥3000 mg/kg groups. In females administered metolachlor, the microsomal cytochrome P450 content was increased by 29-58% in the ≥3000 mg/kg groups.

In males administered S-metolachlor, the microsomal EROD and PROD activities were increased by 122-164% and 740-882% in the ≥3000 mg/kg groups, respectively. In males administered metolachlor, the microsomal EROD and PROD activities were increased by 168-191% and 528-896% in the ≥3000 mg/kg groups, respectively. In females administered S-metolachlor, the microsomal EROD and PROD activities were increased by 125-148% and 2971-6100% in the ≥3000 mg/kg groups, respectively. In females administered metolachlor, the microsomal EROD and PROD activities were increased by 120-134% and 2343-4371% in the ≥3000 mg/kg groups, respectively.

In males administered S-metolachlor, the microsomal UDPGT activity was increased by 88-97% in the ≥3000 mg/kg groups. In males administered metolachlor, the microsomal UDPGT activity was increased by 93-155% in the ≥3000 mg/kg groups. In females administered S-metolachlor, the microsomal UDPGT activity was increased by 39-64% in the ≥3000 mg/kg groups. In females administered metolachlor, the microsomal UDPGT activity was increased by 37-71% in the ≥3000 mg/kg groups, respectively.

The overall results of the present investigation demonstrate that metolachlor and S-metolachlor are strong and reversible hepatic enzyme inducers in male and female rats. The ultramorphological and biochemical findings are aligned with treatment-related findings in the 28-day dietary toxicity study (Frankhauser, 1995; MRID 50396001) of increased liver weights and centrilobular hypertrophy.

This non-guideline 28-day study is considered supplemental information, although it was considered acceptable for regulatory purposes. This study, in conjunction with MRID 50396001, is being used to support a cancer mode-of-action for liver tumors with the intended purpose of comparing the effects of treatment with metolachlor (CGA24705) to those of S-metolachlor (CGA77102) in rats.

7. In a non-guideline, 60-day dietary toxicity study (Mainwaring, 2006; MRID 50396003), groups of fifteen female Sprague Dawley [Crl:CD(SD)] rats/treatment period were administered metolachlor (CGA24705, 97.7% a.i.; Batch # P.111072) in the diet at dose levels of 0 or 3000 mg/kg for 3, 5, 7, 14, 28 and 60 days. The primary purpose of this study was to investigate the prospective inductive effect of metolachlor on liver parameters including BrdU incorporation in hepatocytes, hepatocytic apoptosis, biochemical/microsomal enzyme and CYP-450 activities, and CYP-450 protein content.

There were no treatment-related effects on mortality, clinical observations, body weight or body weight gain, daily food consumption or daily food consumption ratio, absolute and relative (to body) kidney weights, hepatocyte labelling indices, hepatocyte apoptosis, lauric acid 11-hydroxylation, or peroxisomal fatty acid ß-oxidation. Decreases in absolute and relative liver weights of 7% on Day 7, minor increases in the plasma activities of aspartate aminotransferase, alkaline phosphatase, and glutamate dehydrogenase on Day 14, increased incidences of hepatocytic reduced glycogen after treatment for 5, 14, 28, and 60 days, reaching significance ($p<0.05$) on Day 60, decreased hepatic microsomal protein content of 20% on Day 14, and decreased lauric acid 12-hydroxylase activity were not regarded as toxicologically and/or biologically relevant.

Treatment with metolachlor at a dietary dose of 3000 mg/kg resulted in increased microsomal cytochrome P-450 concentration (↑30%), and increased activities of microsomal *O*-demethylation of methoxyresorufin (↑62%), *O*-deethylation of ethoxyresorufin (↑93%), *O*-dependentylation of pentoxyresorufin (↑1490%), and *O*-debenzylation of benzyloxyresorufin (1818%) by Day 60.

Treatment with 3000 mg/kg metolachlor for 14 or 60 days increased the total liver microsomal oxidation rate of testosterone by 88% and 149%, respectively, compared to control values.

There was no treatment-related effect on microsomal testosterone 2α-hydroxylation rate up to Day 60. Microsomal testosterone hydroxylation rates were increased at positions 16α (↑1117%) and 16β (↑1019%) by Day 60, with moderate increases in hydroxylation rates at positions 1α, 2β, 6α, 6β, 7α, 15α, and 15β (↑27-228%), as well as increased oxidation from testosterone to androstenedione (↑170%) by Day 60. Moderate increases in epoxide hydrolase, UDPGT, and cytosolic glutathione S-transferase activities of <2-fold also were observed after treatment of up to 60 days.

Finally, immunoblot analyses were conducted with microsomal preparations from Days 14 and 60. Two strong bands corresponding to CYP1Al (peak 1) and CYP1A2 (peak 2) were present with the positive control treated with MAb d15. Mab d15 recognized one protein band with a molecular weight corresponding to CYP1A2 in the control rats. Administration of 3000 mg/kg metolachlor for 14 days demonstrated no treatment-related effect. Treatment for 60 days resulted in a slight increase in the intensity of this band (↑88%) relative to control.

One strong protein band with a molecular weight corresponding to the closely-related cytochrome P450 isoenzymes CYP2B1 and CYP2B2, and a faint band from an unknown, constitutively-expressed cytochrome P450 isoenzyme, were present with the positive control treated with MAb be4. In the liver microsomes from control rats, the band for CYP2B1/2 was not detectable. The very faint band from the unknown, constitutively-expressed cytochrome P450 isoenzyme was present. Administration of 3000 mg/kg metolachlor demonstrated a strong CYP2B1/2 band.

One strong band corresponding to CYP3Al and CYP3A2 was present with the positive control treated with MAb p6. In the liver microsomes from control rats, this antibody recognized a faint band corresponding to CYP3A1/2. Administration of 3000 mg/kg metolachlor resulted in a moderate increase in this band of approximately 300%.

One strong band corresponding to CYP4Al and CYP4A3 was present with the positive control treated with MAb clo4. In liver microsomes of control rats, this antibody recognized one protein band with a molecular weight corresponding to CYP4A1/3. Administration of 3000 mg/kg metolachlor demonstrated no treatment-related response.

The overall results of the present investigation demonstrate, and reconfirm, that metolachlor is a strong hepatic enzyme inducer in rats.

This study is classified Acceptable/Non-guideline and satisfies the intended purpose of assessing the effects of treatment with metolachlor on hepatic parameters in rats.

A.5 Literature Search for Metolachlor

Date and Time of Search: 11/02/2018; 02:39 pm
Search Details: ((*Metolachlor*)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed hits: 94
Number of Swift Articles: 39 for Animal
Number of Swift Articles: 76 for Human
Number of Swift Articles: 0 for No Tag

All studies identified in the PubMed search were screened when the citation list was ≤100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the "Animal" and/or "Human" tag. Note that articles for S-metolachlor were captured in the metolachlor search.

Number of Articles Identified as Relevant for Risk Assessment: 1

Citation of Articles Identified as Relevant for Risk Assessment:

> **Mathias, F. T., Romano, R. M., Sleiman, H. K., de Oliveira, C. A., and Romano, M. A. (2012). Herbicide metolachlor causes changes in reproductive endocrinology of male Wistar rats. ISRN Toxicology. 2012:130846.**

Conclusion of Literature Search: Following a full text review, no studies were identified that contained relevant information (either quantitative or qualitative) that would impact the risk assessment or that would be considered in the selection of Points of Departure (PODs) for the human health risk assessment for Registration Review. The Mathias *et al.* 2012 reference was also identified in an EDSP literature search but was not utilized in the metolachlor EDSP weight-of-evidence analysis (Akerman, G. and Blankenship, A., 6/29/15).

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.
**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize citations lists that were larger than 100. Studies identified in the PubMed search were tagged and grouped based on the model of interest in the study (e.g. human, animal, *in vitro*, etc.).

Appendix B. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1, the AHETF database, the ORETF database, HED's 2012 Residential SOPs (Lawns/Turf and Gardens/Trees), and a registrant-submitted exposure monitoring study (MRID 44339801), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[15].

[15] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix C. Submission of Analytical Standards

The registrant is required to maintain reasonable amounts of the reference standards for metolachlor and S-metolachlor in the NPSR as long as tolerances remain published in 40 CFR §180.368. When necessary, new reference standards or updated certificates of analysis (COAs), should be sent to the Analytical Chemistry Branch (ACB), which is located at Fort Meade, MD. It should be sent to the attention of either Theresa Cole or Thuy Nguyen at the address listed below, along with a letter of transmittal. **Please note that the full 9-digit ZIP Code is required, or the mail will be returned to the registrant.**

USEPA
National Pesticide Standards Repository
Analytical Chemistry Branch/BEAD/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

The letter of transmittal should include the assay of the standard, name of the analytical method used, a statement of principal impurities, purification procedures employed, storage requirements, and special precautions for safe handling. Replacement of standards, or updated COAs, may be required periodically if supplies are exhausted, if the standards expire, or if decomposition occurs during storage. Material Safety Data Sheets (MSDSs) must accompany all analytical standards as specified by the Occupational Safety and Health Administration (OSHA) in 29 CFR §1910.1200.

Appendix D. International Residue Limit Status Sheet.

S-Metolachlor (PC Code 108801)

Summary of US Tolerances, and International Maximum Residue Limits				
Residue Definitions				
U.S. - 40CFR §180.368(a)(2) & d(2) Plant/Livestock**:** Tolerances are established for the combined residues (free and bound) of the herbicide metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] and its metabolites, determined as the derivatives, 2-[(2-ethyl-6-methylphenyl) amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone, each expressed as the parent compound.				
Canada **-** 2-chloro-N-(2-ethyl-6-methylphenyl)-N-[(1S)-2-methoxy-1-methylethyl]acetamide, including the metabolites: 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone.				
Codex **-** None				
Other -				
Commodity	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	US	Canada	Codex	Other
Beet, sugar, leaves	15			
Beet, sugar, molasses	2			
Beet, sugar, roots	0.5	.3 sugar beet roots		
Berry, low growing, subgroup 13-07G, except cranberry	0.4	.1 strawberries		
Brassica, leafy greens, subgroup 4-16B	1.8	.9 bok choy Chinese cabbages, broccoli raab, collards, kales, mustard greens, mustard spinach, rape leaves		
Bushberry subgroup 13-07B	0.15	.15 Aronia berries, buffalo currant, Chilean guava, currants, elderberries, European barberries, gooseberries, highbush blueberries, highbush cranberries, honeysuckle, huckleberries, jostaberries, lingonberries, lowbush blueberries, native currants, salal berries, Saskatoon berries (Juneberries), sea buckthorn.		
Caneberry subgroup 13-07A	0.1			
Carrot, roots	0.4	.4 carrot roots		
Cattle, fat	0.02			
Cattle, kidney	0.2	.2 kidney of cattle		
Cattle, liver	0.05	.05 liver of cattle		
Cattle, meat	0.02	.02 meat of cattle		
Cattle, meat byproducts, except kidney and liver	0.04			
Cilantro, leaves	8			
Coriander, seed	0.13			
Corn, field, forage	40			
Corn, field, grain	0.1	.1 corn		
Corn, field, stover	40			
Corn, pop, grain	0.1			
Corn, pop, stover	40			
Corn, sweet, forage	40			
Corn, sweet, kernel plus cob with husks removed	0.1			
Corn, sweet, stover	40			

Summary of US Tolerances, and International Maximum Residue Limits				
Residue Definitions				
Cotton, gin byproducts	4			
Cottonseed subgroup 20C	0.1			
Egg	0.02	.02 eggs		
Grain, aspirated fractions	0.7			
Goat, fat	0.02			
Goat, kidney	0.2			
Goat, liver	0.05			
Goat, meat	0.02	.02 meat of goat		
Goat, meat byproducts, except kidney and liver	0.04			
Grass, forage	10			
Grass, hay	0.2			
Horse, fat	0.02			
Horse, kidney	0.2			
Horse, liver	0.05			
Horse, meat	0.02			
Horse, meat byproducts, except kidney and liver	0.04			
Kohlrabi	0.6			
Leaf petiole vegetable subgroup 22B	0.1	.1 cardoon, celery, Chinese celery, fuki, rhubarb, udo, zuiki		
Lettuce	1.5			
Milk	0.02	.02 milk		
Onion, bulb, subgroup 3-07A	0.1			
Onion, green, subgroup 3-07B	2			
Peanut	0.2	.2 peanuts		
Peanut, hay	20			
Peanut, meal	0.4			
Poultry, fat	0.02			
Poultry, meat	0.02	.02 meat of poultry		
Poultry, meat byproducts	0.05	.05 liver of poultry		
Safflower, seed	0.1			
Sesame, seed	0.13			
Sheep, fat	0.02			
Sheep, kidney	0.2			
Sheep, liver	0.05			
Sheep, meat	0.02	.02 meat of sheep		
Sheep, meat byproducts, except kidney and liver	0.04			
Sorghum, grain, forage	1			
Sorghum, grain, grain	0.3			
Sorghum, grain, stover	4			
Sorghum, sweet, stalk	4			
Soybean, forage	5			
Soybean, hay	8			
Soybean, seed	0.2			
Spinach	0.5			
Stalk and stem vegetable subgroup 22A, except kohlrabi	0.1	.1 asparagus		
Stevia, dried leaves	15			

Summary of US Tolerances, and International Maximum Residue Limits				
Residue Definitions				
Sugarcane, cane	0.2			
Sugarcane, molasses	1.5			
Sunflower, meal	1			
Sunflower subgroup 20B	1			
Swiss chard	0.15			
Tomato, paste	0.3			
Vegetable, Brassica, head and stem, group 5-16	0.6			
Vegetable, cucurbit group 9	0.5	.5 balsam apples, balsam pears, cantaloupes, chayote fruit, Chinese cucumbers, Chinese waxgourds, Citron melons; cucumbers, edible gourds, muskmelon, pumpkins, summer squash, watermelon, West Indian gherkins, winter squash.		
Vegetable, foliage of legume, except soybean, subgroup 7A	15			
Vegetable, fruiting, group 8-10, except tabasco pepper	0.1	.1 African eggplants, bell peppers, bush tomatoes, coconas, currant tomatoes, eggplants, garden huckleberries, goji berries, groundcherries, martynias, naranjillas, nonbell peppers; okras, pea eggplants, pepinos, roselles, scarlet eggplants, sunberries, tomatillos, tomatoes, tree tomatoes.		
Vegetable, leaves of root and tuber, group 2, except sugar beet	2	.8 garden beet tops and oriental radish tops		
Vegetable, legume, group 6	0.3	.3 dry beans, dry lima beans, edible-podded snap beans, edible-podded soybeans, peas, succulent shelled lima beans. .2 dry soybeans		
Vegetable, root, except sugar beet, subgroup 1B, except carrot	0.3	.6 parsnip roots .3 garden beet roots, oriental radish roots. .1 rutabaga roots		
Vegetable, tuberous and corm, subgroup 1C	0.2	.2 potatoes, sweet potato roots		
Completed: S. Keel; 7/24/2019 using Global MRL				

Appendix E. Use Profile Tables.

Table E.1 Summary of Directions for Registered Uses of Metolachlor.

Application Timing, Type, and Equipment	Max Single Application Rate	Max Seasonal or Yearly Application Rate	PHI (days)	Use Directions and Limitations
Beans				
Preemergence; Broadcast; Aerial, Ground, Chemigation, Soil broadcast and Soil Incorporation Treatment	From 19713-548 2.0 lb ai/A (2.0 pt product/ A) or 0.2 lb ai/ gal	3.0 pt product/A/year	120	EPA Reg. Nos. EC-19713-548; SC/L-60063-24 24-hr REI.
Corn (field, pop, sweet)				
Broadcast; Aerial, Ground, Chemigation, and soil incorporation	From 19713-549 2.67 lb ai/A (2.75 pt product/ A) or 0.267 lb ai/ gal	NS	30 or 60 day PGI and PFI	EPA Reg. Nos. ECs-19713-547, 19713-549, 60063-22, 60063-24, 60063-48, SLN Reg. Nos.-LA110008, MS120002 12-24-hr REI.
Cotton				
Broadcast; Aerial, Ground, Chemigation, and soil broadcast and banded, and soil incorporation	From LA and MS 2.1 lb ai/A (2.1 pt product/ A) or 0.21 lb ai/ gal [1.32 lb ai/A from 19713-548]	NS	NS	EPA Reg. Nos. ECs-19713-548, 60063-24, SLN Reg. Nos.-LA110008, MS120002 Do not use on sands or loamy sand. 24-hr REI.
Peanuts				
Broadcast; Aerial, Ground, and soil incorporation, lay-by	From 19713-548 2.0 lb ai/A (2.0 pt product/ A) or 0.2 lb ai/ gal Soil inc. treatments 1.32 lb ai/A	NS	90 [30 day PGI and PFI]	EPA Reg. Nos. ECs-19713-548, 60063-24 24-hr REI.
Peas (unspecified)				
Broadcast; Aerial, Ground, Chemigation, and soil incorporation	From 19713-548 2.0 lb ai/A (2.0 pt product/ A) or 0.2 lb ai/ gal	3.0 pt product/A/year	120	EPA Reg. Nos. ECs-19713-548, 60063-24 24-hr REI.
Potato, white/irish or unspecified				
Broadcast; Aerial, Ground, Chemigation, and soil incorporation, lay-by	From 19713-548 2.75 lb ai/A (2.75 pt product/ A) or 0.275 lb ai/ gal Soil inc. treatments 2.0 lb ai/A	3.7 pt product/A/year	40 - 60	EPA Reg. Nos. ECs-19713-548, 60063-24, 60063-52 24-hr REI.
Safflower				

Table E.1 Summary of Directions for Registered Uses of Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**Use Directions and Limitations**
Broadcast; Aerial, Ground, Chemigation, and soil incorporation	From 19713-548 2.0 lb ai/A (2.0 pt product/ A) or 0.2 lb ai/ gal	NS	NS	EPA Reg. Nos. ECs-19713-548, 60063-24 24-hr REI.
Sorghum				
Broadcast; Aerial, Ground, Chemigation, and soil incorporation	From 19713-548 1.67 lb ai/A (1.67 pt product/ A) or 0.167 lb ai/ gal	1 application per year	NS	EPA Reg. Nos. ECs-19713-548, 60063-24 24-hr REI.
Soybeans				
Broadcast; Aerial, Ground, Chemigation, and soil incorporation	From 19713-548 2.75 lb ai/A (2.75 pt product/ A) or 0.275 lb ai/ gal	2.75 lb ai/A/ year (2.75 pt product/A/ year)	30 -90 day PGI and PFI	EPA Reg. Nos. ECs-19713-548, 60063-24, 60063-52, SLN Reg. Nos.-LA110008, MS120002 24-hr REI.
Tomato				
Ground broadcast and directed, and soil banded and soil incorporation	From 19713-548 2.0 lb ai/A (2.0 pt product/ A) or 0.1 lb ai/ gal	2.0 lb ai/A/ year (2.0 pt product/A/ year)	90	EPA Reg. Nos. ECs-19713-548, 60063-24 24-hr REI. Dilute in 20 gallons of water per acre.
Dry Bulk Fertilizer				
Impregnation Equipment and Tractor Drawn Spreader	2.75 lb ai/A or 27.5 lb ai/ton fertilizer	NS	NA	Apply 200-700 lbs of fertilizer mixture per acre. EPA Reg. Nos. ECs-19713-548, 19713-549

PHI: pre-harvest interval, EC: emulsifiable concentrate, SC/L: soluble concentrate/liquid, REI: re-entry interval, SLN: special local need, NS: not stated, NA: not applicable, PGI: pre-grazing interval, PFI: pre-feeding interval.

Table E.2 Summary of Directions for Registered Uses of S-Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**EPA Registration Number (EPA Reg. No.) and Use Directions and Limitations**
Corn				
Preplant, preemergence, postemergence; Broadcast; Aerial, Ground, and Chemigation, Soil Incorporated, Bulk Fertilizer	EC- 2.48 lb ai/A (2.6 pt product/ A) or 0.248 lb ai/ gal	3.71 lb ai/A. year (3.9 pt product/A/ year)	30-60, [30-60 PGI and PFI]	24-hr REI. EPA Reg. No. EC's: 100-816, 100-964, 100-965, 100-1148, 100-1152, 100-1161, 100-1165, 100-1185, 100-1201, 100-1282, 100-1442, 100-817, 100-827, 1381-199. SLNs have 12-hr REI.
Preplant, preemergence; Broadcast, Banded; Aerial, Ground, or Soil Incorporated	G - 2.4 lb ai/A (15 lb product/ A)	2.4 lb ai/A/ year (15 lb product/ A/year)	30 sweet corn, [30 day PGI and PFI (all types)]	24-hr REI. G – 100-910.
Cotton				

Table E.2 Summary of Directions for Registered Uses of S-Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**EPA Registration Number (EPA Reg. No.) and Use Directions and Limitations**
Postemergence; Broadcast; Aerial, Ground, Chemigation, and Soil Incorporated	1.59 lb ai/A (1.67 pt product/A) 0.159 lb ai/ gal	2.48 lb ai/A/year (2.6 pt product/ A/year)	100 Over-the-top postemergence; 80 directed-postemergence	Do not apply on sand or loamy sand soils, or in areas where water is likely to "pond" over the bed. Do not apply on Taloka silt loam. Do not use in Gaines County, TX. Do not graze or feed forage or fodder from cotton to livestock. 24-hr REI. EPA Reg. No. All EC's: 100-816, 100-964, 100-965, 100-1185, 100-1268.
Crop Group 2 Leaves of Root and Tuber Vegetable (except sugarbeet): garden beet, edible burdock, carrot, bitter cassava, sweet cassava, celeriac, turnip-rooted chervil, dasheen (taro), parsnip, radish, oriental radish (daikon), rutabaga, black salsify, turnip, sweet potato, tanier, and true yam.				
Preplant, preemergence; Broadcast, banded; Aerial, Ground, Chemigation, Soil Incorporation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	1.27 lb ai/A (1.33 pt product/ A)	SLNs Turnip - 30	Make only 1 application per year. Banded applications may also be used. Harvest crops at normal timing. 24-hr REI. EPA Reg. No. EC: 100-816
Chicory: Postemergence; Broadcast; SLN-Carrot: preemergence, postemergence; Broadcast, Banded; Aerial, Ground, and Chemigation	1.91 lb ai/A (2.0 pt product/ A) or 0.191 lb ai/ gal	1.91 lb ai/A/year (2.0 pt product/ A/year)	60-64	May be applied postemergence to the chicory crop but before target weed emergence. If an application was made prior to chicory emergence (preplant incorporated, preplant non-incorporated, or preemergence), do not make a postemergence application in the same year. 24-hr REI.
Crop Group 4-16B Brassica Leafy Greens (except watercress and Chinese broccoli): arugula, broccoli raab, Abyssinian cabbage, seakale cabbage, Chinese cabbage (bok choy), collards, garden cress, upland cress, hanover salad, kale, leaves, maca, mizuna, mustard greens, radish leaves, rape greens, wild rocket, shepherd's purse, turnip greens, cultivars varieties and hybrids of these.				
Preplant, preemergence, or Postemergence; Broadcast; Aerial, Ground, and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	1.27 lb ai/A/year (1.33 pt product/ A/year)	30	Banded applications may also be used to treat row middles. Make only 1 application per year. 24-hr REI.
Crop Group 5-16 Brassica Head and Stem Vegetable: broccoli, Brussels sprouts, cabbage, Chinese cabbage (napa), cauliflower, cultivars varieties or hybrids of these. Directions also applicable to Chinese broccoli and kohlrabi.				
Transplanted or Direct-Seeded Crops, Postemergence; Broadcast, directed; Aerial, Ground, and Chemigation	1.9 lb ai/A (2.0 pt product/ A) or 0.19 lb ai/ gal	1.9 lb ai/A/year (2.0 pt product/ A/year)	60	Transplanted crops: applied via ground equipment prior to transplanting or as a broadcast non-incorporated application within 48 hours after transplanting. Banded applications may also be used to treat row middles. Direct-seeded crops: may be applied to soil surface after planting but before weeds or crop emergence or as a broadcast postemergence spray. Make only 1 application per year. 24-hr REI.

Table E.2 Summary of Directions for Registered Uses of S-Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**EPA Registration Number (EPA Reg. No.) and Use Directions and Limitations**
Crop Group 6 Legume Vegetables				
Preplant, preemergence; Broadcast, Aerial and Ground	1.5 lb ai/A (4.0 pt product/ A) or 0.15 lb ai/ gal	1 application per year	120	24-hr REI. EPA Reg. No. EC's: 100-1185
Bean, Peas, and Lentils: Preplant, preemergence; Broadcast, Aerial, Ground, and Chemigation, Soil Incorporated	1.9 lb ai/A (2.0 pt product/ A) or 0.19 lb ai/ gal	1.9 lb ai/A (2.0 pt product/ A)	120, [60 day PFI]	24-hr REI. EPA Reg. No. All EC's: 100-816, 100-964, 100-965, SLN ECs or SC/L
Crop Group 8-10 Fruiting Vegetables (Excluding Okra)				
Preplant, preemergence, postemergence, post-transplant; Broadcast, directed, banded, Aerial, Ground, Chemigation (Tomato Ground and Soil Incorporated only)	1.6 lb ai/A (1.67 pt product/ A) Tomato: 1.91 lb ai/A (2.0 pt product/ A) or 0.096 lb ai/ gal	NS	60-90	24-hr REI. EPA Reg. No. All EC's: 100-816, 100-1185 SLNs 60-90 day PHI Tomato: apply in minimum of 20 gallons of water per acre for ground equipment.
Crop Group 9 Curcubit Vegetables (Melons)				
Preemergence, pretransplant, post emergence; Broadcast, banded; Aerial, Ground, and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	2 apps per season max	30 - 60	24-hr REI. EPA Reg. No. EC: 100-816
Crop Group 13-07G (Excluding Cranberry)				
Preplant, pretransplant or Postemergence; Broadcast, banded; Aerial, Ground, and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	2.4 lb ai/A/year (2.5 pt product/A/ year)	30	24-hr REI.
SLN – Banded; Ground	1.9 lb ai/A (2.0 pt product/A) or 0.19 lb ai/ gal Blueberry (1.27 lb ai/A) Strawberry (0.95 lb ai/A)	NS	28	Caneberry, blackberry, rasberry, blueberry, strawberry. 24-hr REI. EPA Reg. No. EC, NY110004. (Blueberry All ECs, IN130003, MI110004, NJ110012, NY110004, OH110002, OR110005, WA120002, Strawberry OR180010)
Crop Group 22A Stem and Stalk Vegetable (except celtuce, Florence fennel, and kohlrabi): agave, aloe vera, asparagus, bamboo shoots, edible fern (fiddlehead), sea kale, palm hearts, prickly pear pads, Texas prickly pear pads, cultivars varieties and hybrids of these.				
Post-Harvest Treatment; Broadcast; Aerial, Ground, and Chemigation	1.9 lb ai/A (2.0 pt product/ A) or 0.19 lb ai/ gal	1.9 lb ai/A/year (2.0 pt product/ A/year)	16 (Asparagus)	Apply a single broadcast treatment after the harvest season, or to a dormant established crop in the spring or prior to crop emergence in the spring. Banded applications may also be used. Make only 1 application per year. 24-hr REI.

Table E.2 Summary of Directions for Registered Uses of S-Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**EPA Registration Number (EPA Reg. No.) and Use Directions and Limitations**
Crop Group 22B Leaf Petiole Vegetable: cardoon, celery, Chinese celery, fuiki, rhubarb, udo, zuiki, cultivars varieties and hybrids of these. Directions also applicable to celtuce and Florence fennel.				
Preemergence or Postemergence; Broadcast, banded; Aerial, Ground, and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	1.27 lb ai/A/year (2.0 pt product/ A/year)	62	Apply as broadcast preemergence to the soil surface or as a post emergence treatment. Banded applications may also be used. Make only 1 application per year. 24-hr REI.
Transplanted Celery; Preplant Surface, Preplant incorporated, or Postemergence; Broadcast; Aerial, Ground, and Chemigation	1.9 lb ai/A (2.0 pt product/ A) or 0.19 lb ai/ gal	1.9 lb ai/A/year (2.0 pt product/ A/year)	62	Apply as broadcast preplant surface applied or as a preplant incorporated application prior to transplanting or broadcast postemergence application after transplanting. Multiple applications to the same crop are allowed, but the total amount used must not exceed 1.9 lb ai/A/year. 24-hr REI.
Dry Bulk Fertilizer				
Impregnation Equipment and Tractor Drawn Spreader	2.48 lb ai/A or 24.77 lb ai/ton fertilizer	NS	NA	Apply 200-700 lbs of fertilizer mixture per acre. 100-816, 100-829
Grasses Grown for Seed				
Preemergence; Broadcast, Ground, and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	1 application per year	60 day PGI	24-hr REI. EPA Reg. No. EC: 100-816
Horseradish				
Preemergence; Broadcast, Aerial, Ground, and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	1.27 lb ai/A (1.33 pt product/ A)	NS	24-hr REI. EPA Reg. No. EC: 100-816
Lettuce, Leaf; Head				
Preplant, preemergence, postemergence; Broadcast, banded, Aerial, Ground, and Chemigation	0.95 lb ai/A (1.0 pt product/ A) or 0.95 lb ai/ gal	1.27 lb ai/A (1.33 pt product/ A)	20-25	24-hr REI. EPA Reg. No. EC: 100-816
Peanuts				
Preplant, preemergence, postemergence; Broadcast, Aerial, Ground, Soil Incorporated	EC - 1.91 lb ai/A (2.0 pt product/ A) or 0.191 lb ai/ gal 1.27 lb ai/A soil incorporation	NS	90, [30 day PFI and PGI]	24-hr REI. EPA Reg. No. EC's: 100-816, 100-964, 100-965, 100-1185.
Preplant, preemergence; Broadcast, Banded; Aerial, Ground, or Soil Incorporated	G – 1.92 lb ai/A (12 lb product/ A)	2.4 lb ai/A/ year (15 lb product/ A/year)	NS	24-hr REI. G – 100-910
Potato White/Irish or Unspecified (SLNs Sweet Potato)				

Table E.2 Summary of Directions for Registered Uses of S-Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**EPA Registration Number (EPA Reg. No.) and Use Directions and Limitations**
Preplant, preemergence, postemergence; Broadcast, Aerial, Ground, Chemigation, and Soil Incorporated	EC- 2.48 lb ai/A (2.6 pt product/ A) or 0.248 lb ai/ gal 1.91 lb ai/A Soil incorporation	3.43 lb ai/A/ year (3.6 pt product/A/ year)	40-60	12-24-hr REI. EPA Reg. No. All EC's: 100-816, 100-964, 100-965, 100-1162, 100-1185
Preplant, preemergence; Broadcast, Banded; Aerial, Ground, or Soil Incorporated	G – 2.4 lb ai/A (15 lb product/A)	2.4 lb ai/A/ year (15 lb product/ A/year)	60	24-hr REI. G – 100-910
Safflower				
Preplant, preemergence; Broadcast, Aerial, Ground, Chemigation, and Soil Incorporated	1.91 lb ai/A (2.0 pt product/ A) or 0.191 lb ai/ gal	NS	NS	24-hr REI. EPA Reg. No. All EC's: 100-816, 100-964, 100-965
Sorghum				
Preplant, preemergence, postemergence; Broadcast, Aerial, Ground, Chemigation, and Soil Incorporated, Bulk fertilizer	Ground - 1.68 lb ai/A (2.5-2.7 pt product/ A, 100-1152, 100-1442) or 0.168 lb ai/ gal Aerial, Chemigation, Soil Incorporation, Bulk Fertilizer 1.60 lb ai/A (1.67-2.58 lb product/A) or 0.16 lb ai/ gal	1 application per year	60-75, [60 day PGI]	24-hr REI. EPA Reg. No. EC's: 100-816, 100-964, 100-965, 100-1162, 100-1185 FlC – 1381-199
Soybeans				
Preplant, preemergence, postemergence; Broadcast, Aerial, Ground, Chemigation, and Soil Incorporated	EC - 2.48 lb ai/A (2.6 pt product/ A) or 0.248 lb ai/ gal	2.48 lb ai/A (2.6 pt product/ A)	40-60	12-24-hr REI. EPA Reg. No. EC's: 100-816, 100-964, 100-965, 100-1162, 100-1185, 100-1268, 100-958
Preplant, preemergence; Broadcast, Banded; Aerial, Ground, or Soil Incorporated	G – 2.4 lb ai/A (15 lb product/ A)	2.4 lb ai/A/ year (15 lb product/ A/year)	NS	24-hr REI. G – 100-910
Stevia				
Postemergence; Broadcast; Aerial, Ground, and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	3.81 lb ai/A/year (4.0 pt product/ A/year)	30	Make no more than 2 applications prior to harvest of stevia or in the first year of stevia production. Make no more than 3 applications in stevia that have been established for one year or more. Do not apply more than 2.54 lb ai/A in the first year of stevia production. 24-hr REI. EPA Reg. No. 100-816
Sugarbeet				

Table E.2 Summary of Directions for Registered Uses of S-Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**EPA Registration Number (EPA Reg. No.) and Use Directions and Limitations**
Postemergence; Broadcast, Aerial, Ground, and Chemigation	1.59 lb ai/A (1.67 pt product/ A) or 0.159 lb ai/ gal	2.48 lb ai/A (2.6 pt product/ A	60	24-hr REI. EPA Reg. No. EC's: 100-816, 100-1185
Preplant, preemergence; Broadcast, Aerial, Ground, Chemigation, and Soil Incorporated	1.91 lb ai/A (2.0 pt product/ A) or 0.191 lb ai/ gal	3.81 lb ai/A/ year (4.0 pt product/A/ year)	60	24-hr REI. SLN Reg. No. EC: MN040002
Sugarcane				
Preplant, preemergence, postemergence; Groundboom	0.93 – 2.33 lb ai/A (1.5 – 3.75 qt product/A) or 0.233 lb ai/ gal	5.25 qt product/A (3.27 lb ai/A)	100	Do not apply this product through any type of irrigation system. Do not use aerial application to apply this product. Apply in a spray volume of 10-80 gallons/Acre. 24-hr REI. EPA Reg. No. EC - 100-1442
Sunflower				
Preplant, preemergence; Broadcast, Aerial, Ground, Chemigation, and Soil Incorporated	1.91 lb ai/A (2.0 pt product/ A) or 0.191 lb ai/ gal	NS	NS	24-hr REI. EPA Reg. No. EC's: 100-816, 100-1185
Swiss Chard				
Preplant, preemergence, or Postemergence; Broadcast; Aerial, Ground, and Chemigation	Preplant/ Preemergence: 1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal Postemergence: 0.64 lb ai/ A (0.67 pt product/ A)	1.9 lb ai/A/year (2 pt product/ A/year)	40 or 62	Do not apply more than 1.33 pt/A (1.27 lb ai/A) prior to crop emergence. Postemergence applications may be made as a broadcast foliar application when swiss chard has a minimum of 2 true leaves. May be applied postemergence to the swiss chard crop but before target weed emergence. Banded applications may also be used. 24-hr REI. If more than 0.64 lb ai/A was applied PHI=62 days If 0.64 lb ai/A or less was applied PHI=40 days. EPA Reg. No. 100-816
Turf, Sod Farms, Landscape Plantings/Ornamentals, Nurseries, and Container Grown Plants				
Preemergence; Aerial, Ground, and Chemigation	2.48 lb ai/A (2.6 pt product/ A) or 0.248 lb ai/ gal	4.0 lb ai/A/year (4.2 pt product/ A/year)	NA	EPA Reg. No. 53883-149, 100-950 Labels state Not for Homeowner Use Do not apply to trees or plants that will bear harvestable fruit within 12 months. 24-hr REI
Alfalfa (SLN Specific)				
Preemergence; Broadcast, Ground and Chemigation	3.17 lb ai/A (3.33 pt product/ A) or 0.159 lb ai/ gal	NS	NS	24-hr REI. EPA Reg. No. EC: ID020001, NV990006, OR040007 Apply in a minimum of 20 gallons of water per acre

Table E.2 Summary of Directions for Registered Uses of S-Metolachlor.				
Application Timing, Type, and Equipment	**Max Single Application Rate**	**Max Seasonal or Yearly Application Rate**	**PHI (days)**	**EPA Registration Number (EPA Reg. No.) and Use Directions and Limitations**
Crop Group 3 Bulb Vegetables (garlic) (SLN Specific)				
Postemergence; Broadcast, banded, Aerial, Ground and Chemigation, soil incorporation	1.27 lb ai/A (1.33 pt product/ A) or 0.064 lb ai/ gal	2.67 pt product /A/year	21 60 – garlic, onion	24-hr REI. EPA Reg. No. ECs: IN130003, MI110004, OH110002 Apply by ground in minimum 20 gallons per acre KS170001
Coriander (SLN Specific)				
Preemergence, preplant; Broadcast, Aerial, Ground and Chemigation	0.95 lb ai/A (1.0 pt product/ A) or 0.095 lb ai/ gal	NS	30	24-hr REI. EPA Reg. No. EC: IN130003
Okra (SLN Specific)				
Pretransplant, posttransplant; Broadcast, banded, Aerial and Ground	1.91 lb ai/A (2.0 pt product/ A) or 0.191 lb ai/ gal	NS	60	24-hr REI. EPA Reg. No. ECs: IN130003, MI110004, OH110002
Subgroup 4-16A Leafy Green Vegetables (SLN Specific)				
Preemergence, postemergence; Broadcast, banded, directed, Aerial, Ground and Chemigation	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	NS	30 Spinach - 40	24-hr REI. EPA Reg. No. EC: IN130003, MI110004, OH110002, TN110004
Sesame (SLN Specific)				
Preemergence, postemergence; Broadcast, banded, Aerial and Ground	1.27 lb ai/A (1.33 pt product/ A) or 0.127 lb ai/ gal	NS	100	24-hr REI. EPA Reg. No. EC: IN130003, MI110004, OH110002, TN110004
Conservation Reserve Program (CRP) (SLN Specific)				
Pre-emergent, Broadcast, Aerial, Ground, and Chemigation	1.91 lb ai/A (2.0 pt product/ A) or 0.191 lb ai/ gal	2.0 pt product/ A/year	NA	24-hr REI. EPA Reg. No. EC: IA170001

PHI: pre-harvest interval, EC: emulsifiable concentrate, G: granule, SC/L: soluble concentrate/liquid, FlC: flowable concentrate, REI: re-entry interval, SLN: special local need, NS: not stated, NA: not applicable, PGI: pre-grazing interval, PFI: pre-feeding interval.

Appendix F. Risk Estimate Summary Tables.

Table F.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Metolachlor.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)[1] Level of PPE or Engineering control	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Inhalation Dose (mg/kg/day)[4]	Inhalation MOE[5]
Mixer/Loader						
Liquid, Aerial, Broadcast	Field crop, typical	0.219 No-R	2.67 lb ai/acre	350 acres	0.00256	650
Liquid, Impregnation, Commercial treatment	Fertilizer, dry bulk, impregnated	0.083 EC	27.5 lb ai/ton	960 tons	0.0274	61
Liquid, Impregnation, On-farm treatment	Fertilizer, dry bulk, impregnated	0.219 No-R	2.75 lb ai/acre	160 acres	0.00121	1400
Liquid, Aerial, Broadcast	Field crop, high-acreage	0.219 No-R	2.74 lb ai/acre	1200 acres	0.009	190
Liquid, Chemigation, Broadcast	Field crop, typical	0.219 No-R	2.67 lb ai/acre	350 acres	0.00256	650
	Field crop, high-acreage	0.219 No-R	2.74 lb ai/acre	350 acres	0.00263	630
Liquid, Groundboom, Broadcast	Field crop, typical	0.219 No-R	2.67 lb ai/acre	80 acres	0.000585	2900
	Field crop, high-acreage	0.219 No-R	2.74 lb ai/acre	200 acres	0.0015	1100
Applicator						
Spray (all starting formulations), Aerial, Broadcast	Field crop, typical	0.0049 EC	2.67 lb ai/acre	350 acres	0.0000573	29000
	Field crop, high-acreage	0.0049 EC	2.74 lb ai/acre	1200 acres	0.000201	8300
Spray (all starting formulations), Groundboom, Broadcast	Field crop, typical	0.34 No-R	2.67 lb ai/acre	80 acres	0.000908	1800
	Field crop, high-acreage	0.34 No-R	2.74 lb ai/acre	200 acres	0.00233	720
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, Commercial treatment	Field crop, typical	1.2 No-R	2.67 lb ai/acre	320 acres	0.0129	130
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, On-farm treatment		1.2 No-R	2.67 lb ai/acre	160 acres	0.00641	260
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, Commercial treatment	Field crop, high-acreage	1.2 No-R	2.74 lb ai/acre	320 acres	0.0131	130

Table F.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Metolachlor.						
Exposure Scenario	**Crop or Target**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Inhalation**	
		Level of PPE or Engineering control			**Dose (mg/kg/day)[4]**	**MOE[5]**
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, On-farm treatment		1.2 No-R	2.74 lb ai/acre	160 acres	0.00658	250
Flagger						
Spray (all starting formulations), Aerial, Broadcast	Field crop, typical	0.35 No-R	2.67 lb ai/acre	350 acres	0.00409	410
	Field crop, high-acreage	0.35 No-R	2.74 lb ai/acre	350 acres	0.0042	400
Mixer/Loader/Applicator						
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Field crop, typical	8.68 No-R	0.267 lb ai/gallon solution	1000 gallons solution	0.029	58
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Field crop, typical	8.68 No-R	0.267 lb ai/gallon solution	1000 gallons solution	0.029	58

1 Registered crops were combined into surrogate groups for the occupational handler assessment. **Field Crop, High Acreage Includes**: Corn (field and pop), Cotton, peanuts, potato, dry bean and pea, soybean, safflower, and sorghum; **Field Crop, Typical Acreage Includes**: Corn (sweet), snap bean, chickpea, green pea, and tomato.
2 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table – Revised November 2016" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline, PPE, Eng. Controls.
3 Based on the registered labels (See Table E.1). Representative crop for high acreage field crop: soybean; typical field crop: corn (sweet).
4 Exposure Science Advisory Council Policy #9.1.
5 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gallon) × Area Treated (acres or gallons/day) ÷ BW (80 kg).
6 Inhalation MOE = Inhalation HED (1.668 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for S-Metolachlor.						
Exposure Scenario	**Crop or Target[1]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Inhalation**	
		Level of PPE or Engineering control			**Dose (mg/kg/day)[5]**	**MOE[6]**
Mixer/Loader						
Granule, Aerial, Broadcast	Field crop, typical	0.825 No-R	2.4 lb ai/acre	350 acres	0.00866	190
	Field crop, high-acreage	0.825 No-R	2.4 lb ai/acre	1200 acres	0.0298	56
Granule, Tractor-drawn Spreader, Broadcast	Field crop, typical	0.825 No-R	2.4 lb ai/acre	80 acres	0.00198	840
	Field crop, high-acreage	0.825 No-R	2.4 lb ai/acre	200 acres	0.00495	340
Liquid, Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	0.219 No-R	2.48 lb ai/acre	60 acres	0.000408	4100
	Orchard/Vineyard	0.219 No-R	1.91 lb ai/acre	350 acres	0.00183	910
	Sod	0.219 No-R	2.48 lb ai/acre	350 acres	0.00238	700
	Field crop, typical	0.219 No-R	2.48 lb ai/acre	350 acres	0.00238	700
Liquid, Impregnation, Commercial treatment	Fertilizer, dry bulk, impregnated	0.083 EC	24.77 lb ai/ton	960 tons	0.0246	68
Liquid, Impregnation, On-farm treatment	Fertilizer, dry bulk, impregnated	0.219 No-R	2.48 lb ai/acre	160 acres	0.00109	1500
Liquid, Aerial, Broadcast	Field crop, high-acreage	0.219 No-R	2.48 lb ai/acre	1200 acres	0.00815	200
Liquid, Airblast, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	0.219 No-R	2.48 lb ai/acre	20 acres	0.000136	12000
	Orchard/Vineyard	0.219 No-R	1.91 lb ai/acre	40 acres	0.000209	8000
Liquid, Chemigation, Broadcast	Orchard/Vineyard	0.219 No-R	1.91 lb ai/acre	350 acres	0.00183	910
	Sod	0.219 No-R	2.48 lb ai/acre	350 acres	0.00238	700
	Field crop, typical	0.219 No-R	2.48 lb ai/acre	350 acres	0.00238	700
	Field crop, high-acreage	0.219 No-R	3.17 lb ai/acre	350 acres	0.00304	550

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for S-Metolachlor.						
Exposure Scenario	**Crop or Target[1]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Inhalation**	
		Level of PPE or Engineering control			**Dose (mg/kg/day)[5]**	**MOE[6]**
	Nursery (ornamentals, vegetables, trees, container stock)	0.219 No-R	2.48 lb ai/acre	60 acres	0.000408	4100
Liquid, Groundboom, Broadcast	Golf course (tees and greens only)	0.219 No-R	2.48 lb ai/acre	5 acres	0.000034	49000
	Landscaping, turf (lawns, athletic fields, parks, etc.)	0.219 No-R	2.48 lb ai/acre	5 acres	0.000034	49000
	Golf course (fairways, tees, greens)	0.219 No-R	2.48 lb ai/acre	40 acres	0.000271	6200
	Field-grown ornamental crops	0.219 No-R	2.48 lb ai/acre	40 acres	0.000271	6200
	Nursery (ornamentals, vegetables, trees, container stock)	0.219 No-R	2.48 lb ai/acre	60 acres	0.000408	4100
	Sod	0.219 No-R	2.48 lb ai/acre	80 acres	0.000543	3100
	Orchard/Vineyard	0.219 No-R	1.91 lb ai/acre	40 acres	0.000209	8000
	Field crop, typical	0.219 No-R	2.48 lb ai/acre	80 acres	0.000543	3100
	Field crop, high-acreage	0.219 No-R	3.17 lb ai/acre	200 acres	0.00174	960
Applicator						
Spray (all starting formulations), Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	0.0049 EC	2.48 lb ai/acre	60 acres	0.00000911	180000
	Orchard/Vineyard	0.0049 EC	1.91 lb ai/acre	350 acres	0.000041	41000
	Sod	0.0049 EC	2.48 lb ai/acre	350 acres	0.0000531	31000
	Field crop, typical	0.0049 EC	2.48 lb ai/acre	350 acres	0.0000531	31000
	Field crop, high-acreage	0.0049 EC	2.48 lb ai/acre	1200 acres	0.000183	9100
Spray (all starting formulations), Airblast, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	4.71 No-R	2.48 lb ai/acre	20 acres	0.00293	570
	Orchard/Vineyard	4.71 No-R	1.91 lb ai/acre	40 acres	0.0045	370

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for S-Metolachlor.						
Exposure Scenario	**Crop or Target[1]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Inhalation**	
		Level of PPE or Engineering control			**Dose (mg/kg/day)[5]**	**MOE[6]**
Spray (all starting formulations), Groundboom, Broadcast	Golf course (tees and greens only)	0.34 No-R	2.48 lb ai/acre	5 acres	0.0000528	32000
	Landscaping, turf (lawns, athletic fields, parks, etc.)	0.34 No-R	2.48 lb ai/acre	5 acres	0.0000528	32000
	Golf course (fairways, tees, greens)	0.34 No-R	2.48 lb ai/acre	40 acres	0.000421	4000
	Field-grown ornamental crops	0.34 No-R	2.48 lb ai/acre	40 acres	0.000421	4000
	Nursery (ornamentals, vegetables, trees, container stock)	0.34 No-R	2.48 lb ai/acre	60 acres	0.000633	2600
	Sod	0.34 No-R	2.48 lb ai/acre	80 acres	0.000844	2000
	Orchard/Vineyard	0.34 No-R	1.91 lb ai/acre	40 acres	0.000325	5100
	Field crop, typical	0.34 No-R	2.48 lb ai/acre	80 acres	0.000844	2000
	Field crop, high-acreage	0.34 No-R	3.17 lb ai/acre	200 acres	0.0027	620
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, Commercial treatment	Field crop, typical	1.2 No-R	2.48 lb ai/acre	320 acres	0.0119	140
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, On-farm treatment	Field crop, typical	1.2 No-R	2.48 lb ai/acre	160 acres	0.00595	280
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, Commercial treatment	Field crop, high-acreage	1.2 No-R	2.48 lb ai/acre	320 acres	0.0119	140
Fertilizer, dry bulk, impregnated, Tractor-drawn Spreader, On-farm treatment	Field crop, high-acreage	1.2 No-R	2.48 lb ai/acre	160 acres	0.00595	280
Granule, Aerial, Broadcast	Field crop, typical	1.3 EC	2.4 lb ai/acre	350 acres	0.0136	120
	Field crop, high-acreage	1.3 EC	2.4 lb ai/acre	1200 acres	0.0468	36
Granule, Tractor-drawn Spreader, Broadcast	Field crop, typical	1.2 No-R	2.4 lb ai/acre	80 acres	0.00288	580
	Field crop, high-acreage	1.2 No-R	2.4 lb ai/acre	200 acres	0.0072	230

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for S-Metolachlor.						
Exposure Scenario	**Crop or Target[1]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Inhalation**	
		Level of PPE or Engineering control			**Dose (mg/kg/day)[5]**	**MOE[6]**
Flagger						
Spray (all starting formulations), Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	0.35 No-R	2.48 lb ai/acre	60 acres	0.000651	2600
	Orchard/Vineyard	0.35 No-R	1.91 lb ai/acre	350 acres	0.00293	570
	Sod	0.35 No-R	2.48 lb ai/acre	350 acres	0.0038	440
	Field crop, typical	0.35 No-R	2.48 lb ai/acre	350 acres	0.0038	440
	Field crop, high-acreage	0.35 No-R	2.48 lb ai/acre	350 acres	0.0038	440
Granule, Aerial, Broadcast	Field crop, typical	0.15 No-R	2.4 lb ai/acre	350 acres	0.00158	1100
	Field crop, high-acreage	0.15 No-R	2.4 lb ai/acre	350 acres	0.00158	1100
Mixer/Loader/Applicator						
Liquid, Backpack, Ground/soil-directed	Orchard/Vineyard	2.58 No-R	0.191 lb ai/gallon solution	40 gallons solution	0.000246	6800
Liquid, Backpack, Broadcast (foliar)	Nursery (ornamentals, vegetables, trees, container stock)	69.1 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00856	190
Liquid, Backpack, Ground/soil-directed	Nursery (ornamentals, vegetables, trees, container stock)	2.58 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00032	5200
Liquid, Backpack, Broadcast (foliar)	Landscaping, trees/shrubs/bushes	69.1 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00856	190
	Landscaping, plants/flowers	69.1 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00856	190
Liquid, Backpack, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	69.1 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00856	190
Liquid, Backpack, Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	2.58 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00032	5200
Liquid, Manually-pressurized Handwand, Broadcast (foliar)	Nursery (ornamentals, vegetables, trees, container stock)	30 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00373	450
	Landscaping, trees/shrubs/bushes	30 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00373	450

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for S-Metolachlor.						
Exposure Scenario	**Crop or Target[1]**	**Inhalation Unit Exposure (µg/lb ai)[2]**	**Maximum Application Rate[3]**	**Area Treated or Amount Handled Daily[4]**	**Inhalation**	
		Level of PPE or Engineering control			**Dose (mg/kg/day)[5]**	**MOE[6]**
	Landscaping, plants/flowers	30 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00373	450
Liquid, Manually-pressurized Handwand, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	30 No-R	0.248 lb ai/gallon solution	40 gallons solution	0.00373	450
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Orchard/Vineyard	8.68 No-R	0.191 lb ai/gallon solution	1000 gallons solution	0.0208	80
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Orchard/Vineyard	8.68 No-R	0.191 lb ai/gallon solution	1000 gallons solution	0.0208	80
Liquid, Mechanically-pressurized Handgun, Broadcast	Golf course (tees and greens only)	1.9 No-R	2.48 lb ai/acre	5 acres	0.000295	5700
	Golf course (fairways, tees, greens)	1.9 No-R	2.48 lb ai/acre	5 acres	0.000295	5700
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Nursery (ornamentals, vegetables, trees, container stock)	8.68 No-R	0.248 lb ai/gallon solution	1000 gallons solution	0.0269	62
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Nursery (ornamentals, vegetables, trees, container stock)	8.68 No-R	0.248 lb ai/gallon solution	1000 gallons solution	0.0269	62
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Landscaping, trees/shrubs/bushes	8.68 No-R	0.248 lb ai/gallon solution	1000 gallons solution	0.0269	62
Liquid, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1.9 No-R	2.48 lb ai/acre	5 acres	0.000295	5700
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Field crop, typical	8.68 No-R	0.248 lb ai/gallon solution	1000 gallons solution	0.0269	62
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Field crop, typical	8.68 No-R	0.248 lb ai/gallon solution	1000 gallons solution	0.0269	62

1 Registered crops were combined into surrogate groups for the occupational handler assessment. **Field Crop, High Acreage Includes:** Corn (field and pop), Cotton, potato, sugar beet, dry bean and pea, soybean, grasses grown for seed, peanut, safflower, sorghum, sugarcane, sunflower, stevia (sunflower family), alfalfa, coriander, and sesame; **Field Crop, Typical Acreage Includes:** Corn (sweet), crop group 2 (sweet potato, radish, turnip, carrot, etc), horseradish, crop group 4-16B (arugula, kale, mustard greens, etc), crop group 5-16 (cabbage, broccoli, cauliflower etc), snap bean, chickpea, green pea, crop group 8-10 (bell pepper, tomato, eggplant, okra etc), crop group 9 (pumpkin, squash winter and summer, cucumber, etc), strawberry, crop group 22A (asparagus), crop group 22B (celery, rhubarb, etc), lettuce, leaf, head, swiss chard, crop group 3 bulb vegetables (onion, garlic), and crop group 4-16A (spinach, swiss chard, lettuce leaf, leafy greens, parsley, etc); **Orchard/Vineyard Crops Include:** blackberry, blueberry, and rasberry.

2 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table – Revised November 2016" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline, PPE, Eng. Controls.

3 Based on the registered labels (See Table E.2). Representative crop for high acreage field crop: soybean or alfalfa; typical field crop: corn (sweet); orchard/vineyard: caneberry, blackberry.

4 Exposure Science Advisory Council Policy #9.1.

5 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gallon) × Area Treated (acres or gallons/day) ÷ BW (80 kg).

6 Inhalation MOE = Inhalation HED (1.668 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).