April 5, 2019

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RE: Post-Meeting Comments of the Methyl Bromide Industry Panel on the North Carolina Department of Environmental Quality Risk Analysis and Acceptable Ambient Level Recommendation for Methyl Bromide

Dear Chairman Augspurger:

The Methyl Bromide Industry Panel ("MBIP"), the National Pest Management Association ("NPMA"), EcoLab Inc., and Western Industries – North, LLC ("Western Fumigation") appreciated the opportunity to submit comments and participate in the April 1 SAB meeting during which the SAB discussed the North Carolina Department of Environmental Quality ("DEQ"), Division of Air Quality's ("DAQ") Risk Analysis and Acceptable Ambient Level Recommendation for Methyl Bromide ("the Report").

We recognize that the SAB has been discussing and considering the Report and the proposed methyl bromide AAL for several months. However, new information revealed at the meeting (for the first time in any public docket or meeting) further shows that DAQ's choice of the IRIS (EPA Integrated Risk Information System) chronic end point as the basis for the AAL is erroneous and inconsistent with the pertinent definition of "chronic" that underlies the AAL regulations. In short, it

is now clear that DAQ's approach to establishing the AAL for methyl bromide under the North Carolina regulations "chronic toxicant" category is erroneous, and apparently based on a misunderstanding of DEQ's own definition of "chronic" exposure. As such, the SAB should reconsider its tentative concurrence with that endpoint value and withhold its consent to the Report until this issue is resolved and thoroughly considered at a future SAB meeting.

Also, on Friday, April 5, 2019, the U.S. Environmental Protection Agency ("EPA") released information that an updated draft human health risk assessment will be released on Monday, April 8, 2019.[1] That draft risk assessment is expected to build on the prior risk assessments from 2006-2012 to address and evaluate acute and chronic exposure endpoints. The assessment is further expected to provide an analysis of the exposures surrounding commodity fumigation facilities like those in North Carolina. In addition to instructing DAQ to correct its apparent failure to consider the existing EPA risk assessments for methyl bromide from 2006-2012, the SAB should wait until that document is available and fully evaluated by the SAB and DAQ to understand its implications before acting on the current Report.

Below, we discuss these issues in more detail, and also provide further comment on other critical questions raised by the SAB members at the April 1, 2019 meeting.[2]

I. THE IRIS CHRONIC REFERENCE CONCENTRATION IS NOT THE CORRECT CHOICE TO INFORM DAQ'S 8-HOUR "CHRONIC" AAL

At the April 1, 2019 meeting, the SAB held a vote on whether to tentatively concur with the DAQ's choice of the EPA IRIS chronic RfC for a North Carolina methyl bromide AAL, but held its final vote open pending further discussion with several members who were not present.

One question which the SAB properly focused on was DAQ's definition of "chronic." The DAQ's Report issued on February 22, 2019, does not include a definition of "chronic" toxicity for which the Report is providing an AAL recommendation. At the meeting, the SAB discussed this gap and properly asked DAQ to clarify the definition of "chronic" toxicity used to establish the AALs. In

[1] https://www.federalregister.gov/documents/2019/04/08/2019-06818/registration-review-draft-human-health-andor-ecological-risk-assessments-for-several-pesticides

[2] The MBIP represents companies which manufacture, distribute, and hold technical and end-use registrations for methyl bromide fumigation products under the Federal Insecticide Fungicide and Rodenticide Act ("FIFRA"). The MBIP reiterates and re-adopts its comments submitted to the panel on March 27.

response, DAQ disclosed that it was relying on a September 1986 document[3] which uses a highly unusual and outdated definition for "chronic" exposure. That document was not posted to the DEQ website or otherwise readily available to the public prior to the April 1 meeting.[4] Likewise, the 1986 document was not referenced or cited in the DAQ Report to the SAB. Therefore, the MBIP and others, including the SAB, were deprived of the opportunity to review and comment on the DAQ Report with a full understanding of what DAQ was attempting to do.

The 1986 document defines several categories of toxicity, including acute irritants, acute systemic toxicants, chronic toxicants, and carcinogens, which form the basis of the AAL regulations. After reviewing this document, it is clear that there is a definitional mismatch between the IRIS RfC "chronic" values which DAQ used in its Report and the pertinent definition in the 1986 document underlying the AAL regulatory categories which DAQ should have used. Relying on an EPA IRIS RfC toxicity value for DAQ's wholly different definition of "chronic" results in a mismatch that is scientifically invalid, and results in an AAL that deviates from DAQ's mandate.

The 1986 document provides the following definition of a chronic toxicant:

> "those chemicals associated with adverse effects only after multiple (>1) or prolonged ***(>8 hrs) exposures.***" (page 8)

This is a highly unusual and outdated definition of a chronic exposure, which is typically defined as a lifetime exposure. The DEQ document was developed in 1986, the early years of the development of risk assessment science. The scientific and regulatory community have settled on a different definition of "chronic" since the time of the 1986 Recommendations document.

Most pertinently, the EPA IRIS program's definition of "chronic exposure" is:

> "Repeated exposure by the oral, dermal, or inhalation route for ***more than approximately 10% of the life span in humans*** (more than approximately 90 days to 2 years in typically used laboratory animal species)."[5]

EPA has further explained that a chronic duration is one that is "for humans at least seven years."[6]

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[3] Report and Recommendations of the Air Toxics Panel of the North Carolina Academy of Sciences to the Division of Environmental Management, North Carolina Department of Natural Resources and Community Development; September 1986 (the "1986 document").

[4] DAQ has since made the full 1986 Report available at: https://files.nc.gov/ncdeq/GenX/SAB/1986-NCAS-Recommendations.pdf.

[5] https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary (emphasis added).

[6] https://www.epa.gov/risk/conducting-human-health-risk-assessment

The stark contrast between these two definitions is readily apparent.[7] It appears that DAQ inappropriately relied on the IRIS "lifetime" value when it should have chosen a toxicity endpoint more relevant to the "8 hour" exposure endpoint required by the 1986 document.

As the MBIP explained in our prior comments, and at the SAB meeting, appropriate data and values are available from authoritative bodies that are relevant to an "8 hour" exposure timeframe. And DAQ should have used one of those values.

EPA generally performs risk assessments with three or more categories of exposure duration and provides the following definitions for acute, subchronic, and chronic:

- Acute - right away or within a few hours to a day
- Subchronic - weeks or months (for humans generally less than 10% of their lifespan)
- Chronic - a significant part of a lifetime or a lifetime (for humans at least seven years)

The DAQ Report uses a U.S. EPA toxicity level (a Chronic Reference Concentration) from IRIS that EPA defines as being for a chronic exposure, (e.g. for "at least seven years"): "An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for a chronic duration (***up to a lifetime***) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects ***during a lifetime***."[8]

Thus, the IRIS Reference Concentration is consistent with EPA's definition of chronic exposure, but not with the North Carolina DEQ definition in the 1986 document on which DAQ is relying. The methyl bromide IRIS RfC is based on a 29-month rat study, equivalent to a lifetime exposure. When performing a risk assessment, the only appropriate exposure duration estimate to compare with this Reference Concentration is a long-term value, not an 8-hour or 24-hour average. No EPA risk assessment would compare the IRIS RfC with an acute exposure timeframe.

The inconsistent definitions of chronic exposure are particularly problematic as DAQ proposes to apply the EPA IRIS lifetime "chronic" toxicity level to air concentration estimates using a dispersion model and a peak 24-hour averaging period to protect against the NC DAQ's 8-hour "chronic" exposure limit. This is both scientifically unsound and unnecessary. As explained below, this mismatch of exposure duration will erroneously overestimate risks.

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[7] To avoid further confusion, the MBIP will in this document refer to the IRIS "chronic" timeframe as a "lifetime" exposure, and the DAQ "chronic" timeframe as "more than 8 hours."
[8] *Id.* (emphasis added)

Based on the DAQ testimony at the SAB meeting, it is our understanding that DAQ intends to rely on a peak 24-hour emission profile and run a dispersion model with five years of meteorological data for purposes of modeling fence line exposure for permitting purposes. Such an exercise will generate 24-hour concentrations at the fence line for each day of the 5-year simulation. DAQ will then use the maximum ("worst case") modeled 24-hour average fence line concentration (over 5 years and in each direction from the facility), or an upper-bound, and compare it to the IRIS lifetime chronic reference concentration. However, such an exercise would result in the state comparing a 24-hour exposure estimate to a federally established reference value for lifetime exposures.

The appropriate way to use dispersion modeling estimates is to separately generate both acute exposure estimates and long-term chronic estimates. For example, EPA and all other states with similar programs first estimate peak 24-hour concentrations in a similar manner to what is described above. Most importantly, the regulator would compare that peak to an *acute toxicity level* appropriate for a 24-hour duration. The regulators would then, separately, compute a long-term average of all 24-hour estimates to generate a long-term (e.g., one year) exposure estimate, and compare that long-term average concentration to the EPA IRIS RfC value or another appropriate *chronic toxicity level.*

Existing and available dispersion models can readily generate the necessary data to make these separate comparisons. Dispersion models output both a 24-hour average concentration and a long-term average concentration from a standard dispersion model run. The EPA Office of Pesticide Programs used similar procedures to estimate risks for methyl bromide for uses such as log fumigations. OPP used the PERFUM model which embeds an EPA dispersion model and is designed to estimate buffer zones. EPA considered both an 8-hour and 24-hour averaging time and established toxicity levels for each exposure duration. It used PERFUM to estimate the distance from the emission source that resulted in concentrations less than the 8-hour and 24-hour toxicity levels. It did not perform modeling to estimate chronic risks for these uses, but it considered the acute risk assessment protective of chronic effects.

As previously explained in the MBIP's prior comments and in our presentations to the SAB, DAQ has made a fundamental scientific error in choosing to rely on lifetime exposure toxicological data when attempting to establish controls for exposures for a much shorter duration such as 8 hours (which is the definition that underlies the AAL "chronic toxicant" category). Given the relevant definition, data appropriate for the selection of short-term toxicological endpoints *must* be used, or the SAB and DAQ risk adopting an AAL that is scientifically unsound and does not comport with the definition underlying the state's regulation.

The SAB should ask DAQ staff to select a toxicological endpoint appropriate to the unique and odd definition of "chronic" which DAQ is using. The EPA IRIS RfC does not fit this definition and is inappropriate.

II. DAQ'S REPORT FAILS TO EVALUATE THE EPA PESTICIDE PROGRAM RISK ASSESSMENTS

During the April 1 meeting, the SAB withheld its consent and recommendations to the entire Report until certain issues and changes had been addressed and made. One of those issues was whether DAQ had properly considered EPA's pesticide program risk assessments for methyl bromide in its Report. When questioned about the EPA risk assessment at the April 1, 2019 meeting, DAQ staff were unable to recall whether or not they had reviewed the EPA pesticide program's risk assessments for methyl bromide. Nonetheless, staff appeared to confirm to the SAB that the Report did not rely on any of the information contained in those risk assessments. This is a glaring and concerning omission. Firstly, the pesticide program analysis is the most recent and comprehensive analysis of methyl bromide risks ever performed by EPA, and it benefited from nearly two decades of more data and research than was available to EPA at the time of the IRIS assessment. Secondly, the EPA analyses and subsequent regulatory actions fully address the same types of exposures which DAQ seeks to regulate.

The MBIP understands that the SAB chose to limit its scope of review to the accuracy of the chronic toxicity endpoint chosen by DAQ for reference. However, DAQ's failure to address the single most comprehensive risk assessment of the exposures DAQ is attempting to review calls into question the conclusions DAQ reached in relying on older and less fulsome data. The SAB should withhold its consent to the conclusions of the report until DAQ provides the SAB with a review of the EPA pesticide program analyses and amends the report to take the EPA's more recent analyses into consideration.

To aid the SAB's analysis of this omission, the MBIP attaches several key decision documents from that risk analysis, as well as the final decision document from EPA's pesticide program for commodity uses of methyl bromide. These documents were previously cited in the MBIP's prior comments, and copies were provided to DAQ and the SAB. A review of these documents will reveal that EPA's expert and decade-long analysis came to significantly different conclusions than DAQ, and that EPA has already adequately addressed and regulated the exposures for which DAQ erroneously stated no regulatory oversight existed. EPA's risk assessments and the "comprehensive" regulatory requirements imposed on applicators were explicitly intended to protect residential bystanders from

the very chronic risks which DAQ asserts are unregulated: "The Agency has concluded that measures to ensure that acute risks are below EPA's level of concern will also mitigate risks for other exposure durations (i.e. short-term, intermediate-term, **and chronic**) to levels below EPA's level of concern." TRED at p. 24-25 (emphasis added).[9]

The MBIP requests that the SAB require the DAQ staff to fully review the EPA pesticide program human health risk assessments, and that the SAB require the DAQ to address those documents in its recommendations. Given the breadth and length of the EPA risk assessments which represent nearly a decade of EPA's attention, it is arbitrary and capricious for DAQ to state that it will fully review and address those risk assessments in less than two weeks as was promised at the SAB meeting.

Further, EPA announced on Friday, April 5, 2019, that a draft updated human health risk assessment will be released on Monday, April 8, 2019. That draft risk assessment is expected to address and evaluate acute and chronic exposure endpoints and is expected to provide an analysis of the exposures surrounding commodity fumigation facilities like those in North Carolina. The SAB and DAQ should wait until that document is available and fully evaluated before acting on the current Report.

In short, MBIP recommends that the SAB ask DAQ to fully review the 2006-2012 EPA risk assessments and the draft risk assessment that will be published on April 8, 2019. The SAB should further instruct DAQ to amend its report as necessary to properly address those risk assessments for discussion by the SAB at the SAB's next regularly-scheduled meeting.

III. DAQ'S REPORT INAPPROPRIATELY ASSUMES CONTINUOUS EMISSION PROFILES

At the April 1 meeting, the SAB also noted that information on the seasonal nature of the fumigation activity for logs should be noted in the Report.[10] The seasonal nature of the U.S. log export industry and fluctuating overseas market demand dictate fumigation activity. Currently, approximately 90% of U.S. log exports are destined for the Chinese domestic market. Chinese regulations require 100% of U.S. logs to be fumigated or debarked in the U.S. before sailing in order to access the Chinese market.

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[9] A more detailed summary of the various bystander protection measures required by the labels was previously provided by EcoLab.

[10] As noted in during the SAB meeting, there are no other industrial uses of methyl bromide except for commodity fumigation, and no remaining soil-fumigation uses in North Carolina.

There are few facilities throughout the U.S. that are able to accommodate the export requirement for fumigation, and these tend to be located near the seaports in order to streamline and create efficiencies in the fumigation process. Fumigation applicators typically batch or group containers of logs that arrive sporadically from various log exporters and conduct a fumigation at a given facility once an optimal number of containers is reached (usually 20-30 containers depending on the size of a given facility). Batching is done to keep costs down for exporters of the highly price-sensitive commodity. The USDA treatment schedules dictate the amount of fumigant used for each container being treated in the batch, an amount which is also dependent on temperature. The higher the temperature, the less fumigant is required. The USDA treatment schedule further dictates the quantity of fumigant based on the type of log. For example, containers of pine logs require 24 hours under fumigant and 24 hours of aeration, using between 15-23 pounds of fumigant per container. Containers of oak logs require 72 hours under gas and 48 hours of aeration, using approximately 42 pounds of methyl bromide/container. While undergoing treatment, the containers are strictly under the control of the fumigator, with no access to the facility by the public. Further, each container of logs is padlocked and placarded with appropriate warning signs to prevent inadvertent access.

Given the maximum allowable usage of 9.9 tons of methyl bromide for a facility under a synthetic minor source permit, a location would be limited to a range of between 476 to 1,480 containers/year, depending on the combination of pine and oak log containers received.

With the seasonal nature of the harvesting of the logs for agricultural reasons, there is little to no fumigation activity during the warmer months. Fumigations are typically performed 6-7 months out of the year.

This seasonal and periodic emissions profile was not addressed or summarized in the DAQ Report and should be more appropriately summarized. It also highlights the fact that DAQ's attempt to use a 24-hour averaging period to address lifetime exposures is misguided as it inappropriately assumes a consistent daily emissions profile, and does not allow for variation between days.

IV. CONCLUSION

Because of the foundational errors in the Report in applying a lifetime RfC to the state's required 8-hour exposure definition, the SAB should require DAQ to address and correct the above issues and the others identified in the MBIP's prior comments before the SAB consents to the Report's recommendations. DAQ's failure to properly evaluate and address the existing robust risk assessments from EPA's pesticide program also must be corrected, and the availability of an updated federal risk

assessment should be considered. DAQ also must properly consider the periodic nature of the emissions from North Carolina facilities.

The MBIP looks forward to helping DAQ and the SAB develop and implement an ambient air level for methyl bromide that is appropriate, effective, and in alignment with accurate and up-to-date science.

Respectfully Submitted,

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Attachments

March 27, 2019

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RE: Comments of the Methyl Bromide Industry Panel on the North Carolina Department of Environmental Quality Risk Analysis and Acceptable Ambient Level Recommendation for Methyl Bromide

Dear Chairman Augspurger and Ms. Hughes:

The Methyl Bromide Industry Panel ("MBIP") submits these comments on the North Carolina Department of Environmental Quality ("DEQ"), Division of Air Quality's ("DAQ") Risk Analysis and Acceptable Ambient Level Recommendation for Methyl Bromide ("the Report").[1]

The MBIP represents companies which manufacture, distribute, and hold technical and end-use registrations for methyl bromide fumigation products under the Federal Insecticide Fungicide and Rodenticide Act ("FIFRA"). The MBIP has been the primary data generator of federally required toxicological data on methyl bromide for the last 30+ years and is uniquely situated to shed light and offer guidance on the science underlying the use of that data. Accordingly, the MBIP looks forward to helping DAQ conduct a rational, science-based review of the methyl bromide toxicological literature as it works to establish recommendations that are both effective and appropriate.[2]

The MBIP appreciates the opportunity to comment on the Report. As more fully explained in the attached Technical Assessment, the analyses and recommendations set forth therein are

[1] The Report was made available for public comment on February 25, 2019 at https://deq.nc.gov/news/press-releases/2019/02/25/state-requests-public-comment-methyl-bromide-report.
[2] The MBIP supports by reference the comments submitted by Ecolab, Inc., Western Fumigation, and the National Pest Management Association.

inconsistent with the best and most up-to-date information and are out of alignment with existing regulatory regimes at both the state and federal level. The comments below, and the attached Technical Assessment, detail several of the most critical errors that permeate the Report and remind DEQ of its statutory mandate. In short, the MBIP has significant concerns that DAQ failed to use the best available science in the creation and development of the recommended AAL as required by North Carolina law.

As it stands, unless the deficiencies and methodological errors identified by the MBIP are corrected, it would be arbitrary and capricious under the North Carolina Administrative Procedure Act for DEQ to act on the recommendations currently presented in the Report. The MBIP recommends that DAQ reconsider the current recommendations in light of the new information presented and revise its work in alignment with the best available science.

I. THE RISKS DAQ IS ATTEMPTING TO REGULATE ARE ALREADY WELL REGULATED

DAQ seems to fundamentally misunderstand the regulatory framework that governs log fumigation operations. DAQ's Report states that the Department's intent is to protect "all persons that may live or work in areas subject to airborne releases of methyl bromide from log fumigation operations" and that "there is no specific federal regulation to protect the public from log fumigation related methyl bromide releases." However, these statements ignore the existence and primacy of EPA's regulation of fumigation under FIFRA.

Because all methyl bromide fumigation products are federally registered pesticides, EPA has chosen to use its FIFRA program as the primary regulatory tool to protect the public from methyl bromide exposures. The residential bystander exposures for which DAQ has conveyed concern have expressly been addressed and mitigated by EPA as part of label amendments within the last ten years. Those label amendments imposed mandatory application procedures and risk mitigation measures to protect bystanders, including residential bystanders. And, labels are binding and legally enforceable regulatory documents that ensure that the actual use of a product is consistent with its approved use. FIFRA § 12(a)(2)(G). Each methyl bromide product clearly bears the warning, "[i]t is a violation of Federal law to use this product in a manner inconsistent with its labeling."

As part of its regulation of fumigation through labeling, EPA required methyl bromide registrants to implement mandatory label requirements for applicators to establish "buffer zones"

around each fumigation site into which bystanders may not enter or be present.[3] In seeking to mitigate fumigation exposures, EPA chose to rely on bystander exclusions zones, or "buffer zones" because they protect both bystanders and workers from methyl bromide exposures that could exceed EPA's level of concern. TRED at p. 25. "[Buffer zones] represent the distances within which all bystanders must be excluded to ensure that their acute exposure to methyl bromide does not exceed the Agency's level of concern. EPA believes that requiring buffers at these distances combined with other mitigation measures described in this document will ensure that exposures will not exceed the Agency's level of concern." TRED at 30.

EPA also required applicators to follow "a comprehensive approach that requires mitigation measures such as fumigation management plans (FMPs), buffer zones, air monitoring, posting and notification, and record keeping, [that] will ensure that acute risks from inhalation exposure to both workers involved in the fumigation process and bystanders in areas around enclosures do not exceed EPA's level of concern." TRED at 25. This "comprehensive approach" was explicitly intended to protect residential bystanders from the very chronic risks which DAQ asserts are unregulated: "The Agency has concluded that measures to ensure that acute risks are below EPA's level of concern will also mitigate risks for other exposure durations (i.e. short-term, intermediate-term, **and chronic**) to levels below EPA's level of concern." TRED at p. 24-25 (emphasis added).[4]

The chronic exposure scenarios which the Report claims are unregulated and which DAQ seeks to protect bystanders from are thus already well regulated, and DAQ's assertion that additional bystander protections are needed is incorrect. DAQ should work with the permit holders to better understand how these label requirements are implemented and how those measures already protect residential bystanders to a very high degree.

II. DAQ'S RECOMMENDED ACUTE EXPOSURE MONITORING LIMIT IS IMPROPERLY DERIVED FROM CHRONIC TOXICOLOGY DATA

As described in more detail in the Technical Assessment attached to this document, DAQ's Report contains significant toxicological errors. Namely, DAQ is recommending that DEQ use an *annual* chronic exposure value as a *24-hour* averaging limit. This choice conflates a chronic exposure

[3] EPA Report of Food Quality Protection Act (FQPA) Tolerance Reassessment and Risk Management Decision for Methyl Bromide, and Reregistration Eligibility Decision (RED) for Methyl Bromide's Commodity Uses (TRED), at p. 24 (August 2006).

[4] A more detailed summary of the various mitigation measures required by the labels has been provided by EcoLab.

end-point with an acute exposure window and therefore would apply a significantly over-restrictive regulatory requirement without providing any public safety benefit.

As more fully explained in the attached Technical Assessment, DAQ's chosen approach is in conflict with established sound science and practice for choosing ambient air monitoring limits. Where, as here, an agency wishes to implement a 24-hour average monitoring window, the appropriate toxicological endpoint for consideration is an acute toxicological endpoint. DAQ's approach contradicts the methods and guidelines for conducting a risk assessment from the authorities on which DAQ relies, as well as commonly accepted practice for risk assessments. All of the guidelines and analyses presented above confirm that a risk analysis must generate any recommendations and/or limits based on data relevant to the same duration of exposure (i.e., acute data for acute exposures; chronic data for chronic exposures).

DAQ's recommendation also ignores factual reality. In effect, by using the chronic year-long RfC as a 24-hour acute limit, DAQ assumes that the permitted fumigation activities emit methyl bromide at a constant rate, 24-hours per day, 365 days per year. This ignores reality and sound practice. As the permit approving body for these facilities, DAQ is well aware that methyl bromide emissions are infrequent and periodic, with some days having higher emissions than others, and many days having no emissions. This means that the chronic (e.g., annual) average ambient air level will be far lower than any particular acute (e.g., one day) ambient air level. This is why the sound regulatory approach used by EPA and other regulatory authorities is to utilize an acute exposure limit for short-term monitoring limits, and to use the chronic RfC for long-term, annual, exposure limits.

As further explained in the Technical Assessment, DAQ should retract and reconsider its current recommendation and develop recommendations that are in accord with accepted scientific practices.

III. ACCEPTANCE OF THE DAQ'S FLAWED AAL RECOMMENDATION WOULD VIOLATE THE NC APA

Under North Carolina law and in alignment with principals of good rulemaking, DAQ must rely on accurate and up-to-date information regarding the characteristics and use of methyl bromide in establishing an Acceptable Ambient Level ("AAL"). DAQ must also apply that data using valid scientific methods. Failing to do so is at odds with DAQ's goal of "providing *science-based* environmental stewardship for the health and prosperity of all North Carolinians

(https://deq.nc.gov/about/history-of-deq) and is contrary to the regulations that govern DAQ's creation of AALs. N.C. Gen. Stat. § 150B-19.1; N.C. Gen. Stat. § 150B-51.

Per the North Carolina Administrative Procedure Act ("APA"), DAQ is required to ensure that rulemakings, including the establishment of an AAL, are "based on sound, reasonably available scientific, technical, economic, and other relevant information." § 150B-19.1(a)(5). If DAQ fails to support its determinations and documents with substantial evidence, its actions will be deemed arbitrary, capricious, and an abuse of discretion. § 150B-51(b)(5)(6).

As set out above, DAQ's Report is based on a fundamental misunderstanding of the existing federal regulations applicable to log fumigations. Further, the state's chosen approach to selecting a 24-hour averaging threshold is in direct contravention to the best available scientific, technical, and other available information. A continuation of this misguided approach to rulemaking on the part of DAQ would violate the requirements of the NC APA.

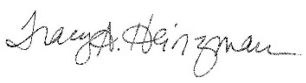
Additionally, although they do not address an un-regulated hazard, the AALs proposed for methyl bromide in the Report are much more restrictive than those involved in EPA's FIFRA processes. The very risks which DAQ claims to be addressing have already been addressed by the U.S. EPA through the enforceable label restrictions. Therefore, there is no actual un-regulated threat to public health, safety, or welfare. DAQ may not impose a more restrictive standard, limitation, or requirement than those imposed by federal law or rule. N.C. Gen. Stat. § 150B-19.3(a).

Finally, North Carolina law mandates that DAQ "reduce the burden upon those persons or entities who must comply with its promulgated rules." N.C. Gen. Stat. § 150B-19.1(a)(2). The Report's substantial decrease in the ambient air levels for methyl bromide would greatly burden the operations of MBIP's members and other methyl bromide stakeholders in North Carolina. However, as laid out above, the decrease serves no real value. Similar statutory regimes in other states do not require such strict ambient air levels for methyl bromide and yet, no great harms have befallen the public or the environment in those jurisdictions. Additionally, the Report's proposed methyl bromide levels are not supported by the large body of science that has developed over the past several decades. Therefore, the levels set out in the Report are disproportionately burdensome in comparison to the to the benefit they confer.

IV. CONCLUSION

Because of the foundational errors in the Report, DAQ must set aside the current recommendations and reconsider the state's approach to these issues. At a minimum, DAQ must recognize the large body of toxicological data not included in the Report and should restart the process of investigating appropriate ambient air levels for methyl bromide. As the registrants of methyl bromide products, the members of the MBIP have generated a significant toxicology database for use by EPA's pesticide program over the past 30+ years and are particularly equipped to help DAQ in this process. The MBIP understands both the science underlying methyl bromide and the day-to-day realities associated with its use. The MBIP looks forward to helping DAQ develop and implement an ambient air level for methyl bromide that is effective and in alignment with accurate and up-to-date science.

Respectfully Submitted,



Tracy A. Heinzman
Executive Director, Methyl Bromide Industry Panel

Attachments

March 27, 2019

Methyl Bromide Industry Panel
Technical Assessment of DAQ Report:
Risk Analysis and Acceptable Ambient Level Recommendation for Methyl Bromide

Vincent J. Piccirillo, Ph.D., DABT[1]
Rick Reiss, M.S., ScD[2]

I. Introduction

The North Carolina Department of Environmental Quality, Division of Air Quality (DAQ) issued a report entitled "Risk Analysis and Acceptable Ambient Level Recommendation for Methyl Bromide" on February 22, 2019. In that document DAQ recommends 5 μg/m^3 methyl bromide (0.005 mg/m^3 or 1 ppbv) in air as the 24-hour N.C. Acceptable Ambient Level (AAL). While 24-hour maximum ambient exposure limits are normally established using acute toxicity data, DAQ has chosen to recommend an AAL set at the chronic reference concentration (RfC) established by the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) program. This approach is flawed and without precedent from any regulatory authority.

The DAQ risk assessment further posits, without substantiation and in contravention to the fumigation practices required by the products' labeling under Federal pesticide law, that persons living adjacent to log fumigation operations may be exposed to fumigants released to the ambient air under exposure frequency and duration conditions that reflect the EPA chronic exposure definition. DAQ is therefore proposing to set the 24-hour averaging time for acute methyl bromide exposure using the same level as that for potential chronic systemic (non-cancer) effects associated with the chronic RfC endpoint; a proposal without precedent from any other federal or state regulatory body.

It appears that DAQ had considered using acute exposure data to set its limit, but the DAQ document inaccurately states that neither the EPA, the EPA's IRIS program, or the ATSDR provide acute health values protective of the general public for methyl bromide inhalation exposures. This statement suggests that DAQ may have been unaware of the EPA reregistration risks assessments and other documents related to methyl bromide's registration review. In these documents EPA clearly recognizes that exposure durations to pesticides can be acute, short/intermediate term, or chronic; and EPA selected toxicological endpoints specifically relevant to each of these exposure durations. To the extent DAQ was not aware of this acute toxicological data, summarized below, DAQ should revisit its approach to establishing its AAL in light of this new data.

In particular for methyl bromide commodity fumigations, it is important to conduct risk assessments and establish acceptable limits of exposure for scenarios that reflect actual use and exposure patterns, and that use the best available science. Establishing limits based on inaccurate assumptions, that do not reflect actual use patterns, and that do not use the best and

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most applicable science and data would represent a significant departure from best risk assessment practices.

The purpose of this document is to address the key areas in the DAQ document that need modification or changes, and to provide certain data of which DAQ may not have been aware:

1. The use of a chronic exposure endpoint for the establishment of 24-hour acute exposure monitoring limits contradicts established and accepted scientific practice
2. A summary of available acute and short/intermediate term toxicological endpoints
3. The apparently overly conservative uncertainty factors used in the risk assessment
4. A summary of available data on the carcinogenic potential of methyl bromide

II. Definitions of Acute and Chronic Exposures

As an initial matter, a fundamental issue presented by the DAQ report is the staff's use of a chronic exposure RfC to inform their choice of a recommended acute exposure limit. This paper will use the below standard and accepted definitions when referring to acute and chronic exposures.

An "acute" exposure is one that one that occurs over one day (24 hours) or less. USEPA (1998).

A "chronic" exposure is one that occurs over a much longer period, for example over lifetime. USEPA (1998). A chronic exposure level is intended to represent and measure the long-term health impacts a particular chemical may have on the human body and is intentionally measured over a long period of time to account for periodic elevated exposures which are likely to be below the short-term acute exposure limit, and also to account for periods of low or no exposure.

III. DAQ's Use of a Chronic Exposure Endpoint to Set an Acute Monitoring Threshold Contradicts Established and Accepted Scientific Practice

DAQ bases its proposal to adopt the IRIS RfC on the assertion that "[p]ersons living adjacent to log fumigation operations may be exposed to fumigants released to the ambient air under exposure frequency and duration conditions that reflect the EPA chronic exposure definition" (p. 1) concluding, "The DAQ identifies the IRIS chronic RfC as the most appropriate and scientifically valid human health value to provide protection for the long-term health of persons in North Carolina, including sensitive subpopulations that may live adjacent to a log fumigation facility that repeatedly releases methyl bromide to the ambient air during operations." (p.1).

While DAQ asserts that their recommendations are based off potential chronic exposures and that recommendations are for "long-term health," the DAQ chooses to apply an AAL exposure duration that corresponds to acute exposures (i.e., 24-hour AAL). This is directly contrary to recommendations and guidelines for risk assessment analysis, as well as precedents set by the EPA and ATSDR – which the DAQ purports to have based its risk assessment and subsequent recommendations upon.

As an initial matter, the exposure at any given location is affected by a number of different factors, such that a 24-hour average ambient air level on any particular day is likely to be significantly different than other days, and the chronic exposure level for the same location.

1. Meteorology: Meteorological conditions greatly influence downwind concentrations. For example, wind direction typically varies from hour to hour and from day to day. Thus, winds will carry a gas emission to different downwind locations at different times. For this reason, the peak exposure at a given location may be much less than the longer-term exposure. Also, atmospheric stability varies with general climatic conditions, time of day, and season. In more stable atmospheres, a given unit of emission will result in relatively higher concentrations than in less stable conditions. Thus, variations in meteorological conditions will result in variability in downwind concentrations.

2. Operation hours: Log fumigations do not occur continuously. On some days, there may be no fumigations, and there are peak periods of fumigation throughout the year.

3. Emissions: The log fumigations include a treatment and aeration phase. Duration treatment emissions are smaller but occur over a longer period. Aeration removes the remaining gas quickly. The downwind concentration peak will likely occur at different locations for emissions during treatment and aeration.

For all of these reasons, the emissions at a given downwind location can vary significantly. Thus, while a peak 24-hour acute concentration might be higher than the target chronic average concentration at the same location, the changes in concentration caused by varying meteorology, operational hours, and emissions which vary from day to day will typically lead to much lower average exposures across the one-year or longer timeframes applicable to chronic exposures.

Indeed, the inappropriateness of conflating a chronic exposure level and an acute exposure level is recognized in the document which provides the instructions for use of the very RfC on which DAQ has chosen to rely. EPA's guidance for the "IRIS methodology for calculation of RfC" instructs:

> Extrapolation from one exposure regimen to another has uncertainties, most of which are not quantified . . . The exposure-health relationship may be dependent on factors, including (1) the number of exposure hours per day; (2) the exposure scenario, that is, continuous versus interrupted (e.g., 1 week of exposure, 1 week of air, 1 week of exposure, etc.), versus intermittent (X hours per day, Y days per week) regimens; (3) the time of endpoint assessment (e.g., acute versus subchronic versus chronic studies or studies with recovery time before observation); (4) the endpoint(s); and (5) the mechanism of toxicity. (USEPA 1994, p. 2-28).

Additionally, discussion of various study methods indicates that acute and short-term exposure durations are not relevant to the calculation of an RfC: "Clinical studies are typically of acute or short duration and therefore, as such, are less useful as the basis of an RfC. . ." (USEPA 1994, p. 2-3)." "Although such [nonepidemiologic] studies for ethical reasons are typically for acute

durations and therefore, by definition, do not meet the criteria for development of a chronic RfC estimate. . .” (USEPA 1994, p. 2-19).

Further, numerous other guidance and instructional documents from EPA and other authoritative sources reiterate and emphasize this admonition.

In the “General Principles for Performing Aggregate Exposure and Risk Assessments” released by EPA in 2001, EPA states:

> In addition to the selection of an appropriate hazard endpoint for each route of exposure (e.g., oral, dermal, inhalation), an aggregate risk assessment should attempt to match the anticipated frequency and duration of exposure with toxicity studies that reflect comparable timing of exposure. For example, if an effect occurs only after several days of chemical dosing (of animals), it would be inappropriate to compare the estimated exposure over a single day with the exposure associated with an effect which requires multiple days to develop. (USEPA, 2001; p. 17).

In the “Framework for Human Health Risk Assessment to Inform Decision Making” released by the EPA in 2014, the document states:

> The exposure assessment component of the analysis plan is developed by drawing on the information, considerations and decisions represented by the conceptual model for human health. Accordingly, the analysis plan describes the exposure assessment elements specified in the conceptual model, including the relevant routes and pathways, frequency and duration of exposures, populations and life stages, and assessment metrics. (USEPA 2014, p. 31).

In the Human Health Risk Assessment for methyl bromide released by EPA in 2006, the risk assessment is stratified by exposure duration with categorizations broken down into acute, short- and intermediate-term inhalation (defined as 1 day to 6 months), and long-term inhalation (>6 months).

Health endpoints are examined for each of the three exposure durations independently (USEPA 2006, Table 4 pp. 15-16). From this analysis, we see that the duration of exposure used to set Human Equivalent Concentration (HEC) values, is equal to the duration of the toxicological studies analyzed.

EPA explained that “[r]isks from acute exposures were calculated using the maximum 24-hour TWA values measured at each station and comparing them to the acute 24-hour (“agricultural”) HEC and not the 8-hour (“commodity”) HEC because these ambient air results are all 24-hour time-weighted averages. Risks for short- and intermediate-term exposures (i.e., same HEC and uncertainty factors apply to both durations) were calculated using the mean of 8 weekly means calculated by DPR for samples taken over the course of the use season and comparing them to the short- and intermediate-term HEC. This approach was taken in order to statistically weigh equally each week’s contribution to the overall seasonal mean because of differing numbers of

samples in some weeks. Concentrations over the course of a season monitored in these studies did not vary extensively so calculation of average concentrations for shorter durations (e.g., 4 weeks) or even the use of an overall mean of all samples would not expected [sic] to be dramatically different than estimates used in this assessment" (USEPA 2006, pp. 46-47).

In a training package developed by Children's Health and the Environment (CHEST), materials indicate:

> "The method used to calculate HAs [Health Advisories] is similar to that for the RfD's using uncertainty factors. Data from toxicity studies with durations of length appropriate to the HA are being developed." (CHEST 2003, p. 19).

In the "Guidelines for Exposure Assessment" published by the EPA in 1992, the following is stated:

> "The frequency and duration of sample collection will depend on whether the risk assessor is concerned with acute or chronic exposures, how rapidly contamination patterns are changing, ways in which chemicals are released into the environment, and whether and to what degree physical conditions are expected to vary in the future." (USEPA 1992, p. 41).

In "Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation" published by EPA in 2014 states:

> "For a given chemical, the appropriate dose metric will also be determined by, and can vary with, the MOA, duration of exposure, and the adverse effect of concern." (USEPA 2014, p. 22).

In conclusion, there is no precedent for the recommendations provided by DAQ (i.e., using a RfC to establish a 24-hour AAL), and DAQ's approach contradicts the methods and guidelines for conducting a risk assessment from the authorities on which DAQ relies, as well as commonly accepted practice for risk assessments. All of the guidelines and analyses presented above confirm that a risk analysis must generate any recommendations and/or limits based on data relevant to the same duration of exposure (i.e., acute data for acute exposures; chronic data for chronic exposures). Further, no other source identified by DAQ (e.g., National Research Council, California Office of Environmental Health Hazards Assessment [OEHHA], National Toxicology Program, etc.) uses toxicological studies from chronic exposures to make recommendations for acute exposure levels. Additionally, none of these sources equate or indicate comparability between acute and chronic exposure limits.

IV. Critical Data on Acute and Short/Intermediate Term Toxicological Endpoints Are Available and Should be Considered

DAQ attempts to justify its use of RfC for an acute monitoring timeframe by alleging that there is insufficient or no acute toxicological information available for Methyl Bromide. This statement is incorrect and ignores a significant and robust body of data available on that very topic. During the pesticide reregistration for methyl bromide products under Federal Insecticide,

Fungicide, and Rodenticide Act (FIFRA), EPA conducted numerous and extensive reviews of acute toxicological data and published numerous publicly available reviews of that data.

A. Acute endpoint for risk assessment

EPA published an initial guidance document entitled Hazard Identification - Toxicology Endpoint Selection (August 11, 1998[3]). This guidance document discusses studies that are relevant acute hazard identification as given below. Although the guidance was specific to oral exposures at the time, the criteria are also relevant to other exposure regimens such as inhalation.

1. The Acute Neurotoxicity Study in Rats which is pertinent because animals receive a single oral dose to which all toxicological effects can be attributed to the single dose received and as multiple dose levels are tested, a NOAEL [No Observable Adverse Effect Level] can be derived for the acute effects. (At the time of publication of the EPA document, acute neurotoxicity studies had not been conducted for most pesticide chemicals and for this reason, other default studies were considered.)

2. Prenatal Developmental Toxicity Studies can be used for acute oral assessments as a presumption can be made that developmental effects could result from a single dose exposure. Developmental toxicity studies were considered relevant as the treatment route is oral, a single dose may be administered at a possible critical point in fetal development and a possible relationship between maternal toxicity and developmental effects may be determined.

3. Other studies such as subchronic, chronic, reproductive or carcinogenicity studies conducted via the oral route are considered if any toxicological effects are seen within the first few days of dosing and can be extrapolated to an acute event. This may include human data as the first priority with supportive findings from animal studies.

Although an acute neurotoxicity (ANT) study by the inhalation route (Driscoll and Hurley, 1993) was conducted with methyl bromide, EPA selected an inhalation developmental toxicity study in rabbits as having the most conservative NOAEL for acute inhalation risk assessment. In the ANT study, rats were exposed to methyl bromide concentrations of 0, 30, 100 or 350 ppm for 6 hours. The NOAEL for neurobehavioral effects was 100 ppm.

The developmental toxicity study (Breslin et. al., 1990) was conducted with pregnant New Zealand white rabbits. The rabbits were exposed for six hours/day on gestation days 7 through 19 to methyl bromide concentrations of 0, 20, 40 or 80 ppm. At 80 ppm, maternal toxicity was seen that included decreased body weight gain and clinical signs of neurotoxicity characterized by right-sided head tilt, ataxia, lateral recumbency and lethargy. Developmental effects were only noted in maternally toxic 80 ppm group and consisted of low incidences of omphalocele, hemorrhaging with or without edema, retroesophageal right subclavian artery, gall bladder

[3] http://nepis.epa.gov/Exe/ZyPDF.cgi/901A0000.PDF?Dockey=901A0000.PDF

agenesis and fused sternebrae. The NOAEL for both maternal neurotoxicity and developmental toxicity was 40 ppm.

EPA evaluated 3 acute exposure scenarios in reregistration which included agricultural bystander (ambient 24-hour exposure), greenhouse/structural and commodity bystander and occupational. Methyl bromide log fumigation fits the commodity bystander scenario. As noted previously, EPA conservatively selected the 40 ppm NOAEL from the Breslin study as the endpoint for acute inhalation exposure. The Agency calculated an HEC for the commodity bystander scenario of 40 ppm using methodology similar to that of DAQ and assigned a 30X uncertainty factor (UF) (3X UF for animal to human extrapolation with dosimetric adjustment, and UF 10 for human variability) to this value. Using the approach of DAQ, this results in an Acceptable Ambient Level (AAL) of 1.3 ppm.

B. Short/intermediate term endpoint for risk assessment.

Similarly, EPA evaluated short/intermediate term exposure which is defined as a few days to several weeks of exposure. Two short/intermediate exposure scenarios were evaluated; agricultural bystander and commodity bystander or occupational exposure.

The toxicologic endpoint for this study was selected from 2 subchronic inhalation neurotoxicity study in beagle dogs. In a subchronic (5- to 7-week) inhalation toxicity study (Newton, 1994), methyl bromide (tech., 100% a.i.) was administered 7 hours/day, 5 days/week to 4 beagle dogs/sex/dose by whole body exposure at target concentrations of 0, 5, 10/150, 25, 50 or 100 ppm (actual mean concentrations 0, 5.3, 11.0/158.0, 26.0, 53.1 or 102.7 ppm). The systemic toxicity NOAEL was 26 ppm. The lowest-observed-adverse-effect level (LOAEL) was 53.1 ppm based on decreased activity.

In a six-week nonguideline inhalation toxicity study (Schaeffer et. al, 2002) specifically designed to evaluate neurotoxicity, four groups of beagle dogs consisting of 4 males and 4 females/group were exposed to methyl bromide by whole body exposure at concentrations of 0, 5.3, 10, and 20 ppm. The exposures were for seven hours/day, five days/week for six weeks(total of 30 exposures). The NOAEL was 5.3 ppm and the LOAEL was 10 ppm based on the absence of proprioceptive placing and the increased incidence of feces-findings (soft, mucoid feces, and/or diarrhea).

EPA selected the 5.3 ppm NOAEL from the Schaeffer study as the endpoint for short/intermediate inhalation exposure. The Agency calculated an HEC for the ambient air bystander scenario of 1 ppm and assigned a 30X uncertainty factor (UF) to this value. Using the approach of DAQ, the resultant AAL is 33 ppb for short to intermediate term exposure. The California Department of Pesticide Regulation (CDPR) also conducted risk assessments for short/intermediate scenarios.

V. Critical Data on Carcinogenicity is Available and Should be Considered

The DAQ document indicated that methyl bromide was "not classifiable as to human carcinogenicity." This judgment was based on the results from an inadequate oral gavage study with methyl bromide and ignores more recent and accurate science.

EPA reviewed the chronic toxicity/carcinogenicity studies for methyl bromide via the inhalation route in rats (Reuzel et. al, 1987) and in mice (NTP, 1992). Based on the results of these studies, EPA has classified methyl bromide as a not likely human carcinogen. (USEPA, 2007; USEPA, 2013).

VI. DAQ Applied Unnecessary Uncertainty Factors in Its Risk Assessment

Further, DAQ's derivation of chronic toxicological endpoints used an additional, and unnecessary, 3X uncertainty factor adjustment, not required by the existing data. This error further exacerbates the problems caused by the issues described above. If DAQ attempts to move forward with an appropriate chronic exposure limit (e.g., a one-year average), the uncertainty factor issue described here must also be corrected.

It appears from the Report that DAQ attempted to use a traditional approach to conducting human health risk assessments as used by international regulatory bodies by the application of UFs to the NOAEL derived from appropriately selected toxicity studies in animals. The primary UFs are the **interspecies** uncertainty factor and the **intraspecies** uncertainty factor. The interspecies UF is intended to account for the uncertainty involved in extrapolating from animal data to humans. The intraspecies UF is intended to account for the potential variation in sensitivity among human populations and subpopulations including infants and children. The standard default value for each of these factors is 10x with the standard application of a total 100x applied to acute and chronic dietary risk assessments or an acceptable Margin of Exposure (MOE) of 100 for occupational exposures. But DAQ appears to have chosen to add an additional, and unnecessary, 3x uncertainty factor.

When conducting inhalation risk assessments, however, the magnitude of the UFs applied is dependent on the methodology used to determine the appropriate point of departure. DAQ's assessment used the LOAEL from the chronic/carcinogenicity inhalation study in rats as the point of departure and calculated an inhalation RfC or HEC. Since the RfC methodology takes into consideration many pharmacokinetic (PK) differences but not pharmacodynamic (PD) differences between species, the UF for interspecies extrapolation may be reduced to 3x (to account for the PD differences) while the UF for intraspecies variation is retained at 10x. Thus, the UF when using the RfC methodology is customarily 30x.

Based on the strength, quality and completeness of the data under evaluation, the application of additional UFs may be required. Specific criteria that may necessitate application of additional UFs include:

- Extrapolation from the LOAEL to a surrogate NOAEL, if an appropriate NOAEL is not identified in the toxicology database.

- Extrapolation from subchronic toxicity study results to chronic exposure to derive a chronic reference dose when appropriate chronic studies are not available.

- An uncertainty factor to account for deficiencies or the absence of key studies or data in the database for the chemical under evaluation.

As no NOAEL was identified for the portal of entry effects observed in the chronic/carcinogenicity inhalation study in rats that was used for the long-term inhalation risk assessment, DAQ assigned an additional 3X uncertainty factor consistent with the extrapolation from a LOAEL to a NOAEL. EPA in its chronic inhalation assessment for methyl bromide similarly applied the 3X uncertainty factor as the effects noted at this dose level (3 ppm) were not severe, an uncertainty factor of 3x was applied for the LOAEL to NOAEL extrapolation. It should be noted that the nasal lesions were related to both concentration and duration of exposure. The NOAEL for the nasal lesions was >90 ppm after one year of exposure, 3 ppm after 24 months of exposure and >3 ppm after 29 months of exposure.

At a February 4, 2019 meeting, DAQ requested from the Scientific Advisory Board thoughts and recommendations on the topic of the range of risk as it is referenced in the *NCSAB Risk Assessment Guidelines* document on the prior SAB's webpage (NCSAB 1997a). As a result, the DAQ document states:

> In response to the EMC's desire for a range of risk values, DAQ further recommends a factor of 3 (3 = the square root of an UF = 10) placed on the IRIS chronic RfC as an appropriate adjustment factor to reduce the potential for adverse health effects to the subpopulation that possess the Phase II GSTT1 enzyme variant that predisposes them to increased neurotoxic effects. This could represent a lower bound in range of AAL values that could be considered by the EMC.

The overall DAQ risk assessment strongly concludes that the IRIS chronic RfC represents the most sensitive endpoint of the range of adverse health effects observed in the current methyl bromide inhalation toxicity database. The finding, damage to the olfactory epithelial tissues leading to degenerative and proliferative lesions, is an effect deemed of concern to public health. DAQ recommended that an additional 3X uncertainty factor as related to subpopulation sensitivity related to Phase II GSTT1 enzyme variant and increased potential for neurotoxicity be included in the assessment. The additional 3X UF is unwarranted for the following reasons:

1. A 10X interspecies UF for human variability has been applied to the nasal olfactory effects. This "interspecies" uncertainty factor is specifically applied for the protection of sensitive populations which would include those with the Phase II GSTT1 enzyme variant

2. The concentration inducing nasal effects is protective of neurotoxicity.

The LOAEL for nasal toxicity from the Reuzel study was 3 ppm and an additional 3X uncertainty factor was applied to the LOAEL resulting in an "estimated" NOAEL of 1 ppm. Neurotoxicity is the most common toxic effect for inhalation exposure for methyl bromide with neurotoxic effects seen throughout the database in all tested species. The NOAEL and LOAEL for studies in which neurotoxicity was assessed by validated Functional Observational Battery (FOB) and motor activity procedures or noted by study clinical signs or histopathological findings are summarized in the following table. It is noteworthy that no clinical signs related to neurotoxicity were noted at methyl bromide concentrations up to 90 ppm (highest tested concentration) in the Reuzel study in which the nasal effects were seen and serves as the basis for the chronic risk assessment.

Study (Reference)[4]	**NOAEL (ppm)**	**LOAEL (ppm)**	**Neurotoxic Effects**
Acute neurotoxicity (Driscoll and Hurley, 1993)	100	350	Decreased activity and alertness as measured in a functional observation battery examination, decreased motor activity and decreased body temperature in males and females were observed. A slight decrease in hind-limb grip strength in males may have been treatment-related.
Subchronic neurotoxicity (Norris et al., 1993)	30	70	Increased mortality (2 animals), convulsions (2 animals affected), effects on several FOB parameters and brain histopathology in males.
Developmental toxicity-rabbit (Breslin, 1990)	40	80	Lethargy, right side head tilt, ataxia and lateral recumbency.
Subchronic dog 1 (Schaefer et al., 2002)	5.3	10	Absence of proprioceptive placing in males.
Subchronic dog 2 (Newton, 1994)	26	53.1	Decreased activity.
Mouse oncogenicity (NTP, 1992)	33	100	Mortality (males), neurological signs (abnormal posture, tremors, ataxia, limb paralysis and emaciation.), decreased body weight/weight gain and microscopic lesions in the brain, heart, sternum and olfactory epithelium.
Developmental neurotoxicity-rat(Beck, 2005)	25	50	Decreased motor activity.

As compared to the "estimated" NOAEL for nasal effects (1ppm), the NOAELS for neurotoxicity findings from these studies clearly demonstrate that the 1ppm values is protective

[4] The MBIP can make copies of studies subject to MBIP's copyright protections available to DAQ and the SAB subject to appropriate protections from public release. The MBIP can also provide copies of EPA's Data Evaluation Records for these studies.

of humans, including sensitive humans, from neurotoxicity. Therefore, the recommended addition of a 3X UF to protect subpopulation sensitivity related to Phase II GSTT1 enzyme variant is not necessary.

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