Updates and GenX Benchmark Dose Progress

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Overview

- Updates
  - EPA Goal
  - Peroxisome Proliferator-Activated Receptor (PPAR)
- Benchmark Dose Progress

EPA Goal

- EPA is working on a GenX goal
- Indicate goal of 5 months, but timing uncertain
- DHHS intending to continue work on benchmark dose modeling

Peroxisome Proliferator-Activated Receptor (PPAR)

- Group of nuclear receptors
- PPARs are activated by a variety of endogenous and exogenous compounds including PFAS
- Regulate genes involved in fatty acid metabolism, inflammation, and proliferation
- Three PPARs in mammals
  - PPARα
    - Highest expression in liver, intestine, kidney, heart, and adipose tissue
  - PPARβ
    - Highest expression in intestinal epithelium, liver, and keratinocytes
  - PPARγ
    - Highest expression in adipose tissue and macrophages

PPARα Mechanism of Action: Relevance to Human Health

- Corton et al.
  - Argues that a number of agents, including PFAS, cause liver tumors in rodents via a mode of action that includes activation of PPARα, and that this MOA is not relevant to humans.

Corton et al. 2018

PPARα Mechanism of Action: Relevance to Human Health

- Some PFAS effects associated with activation of PPARα
- Evidence of interspecies difference in levels of PPARα expression and responsiveness
- PPARα-independent mechanisms also involved in PFOA and PFOS toxicity, including liver toxicity
- Relevance of these endpoints to human health cannot be excluded

EPA Lifetime Health Advisories for PFOA and PFOS; ATSDR's draft ToxProfile for PFAS

Benchmark Dose Modeling Progress

- OEEB staff reviewed 7 studies:
  - Represent all repeat-dose oral toxicity studies
  - Other GenX studies have been reviewed, but were not considered relevant for drinking water exposures
  - Benchmark dose modeling is focused on GenX only
- Data tables were created for each statistically significant endpoint for GenX

Benchmark Dose Modeling Progress

- Seven (7) studies:
  - 28-Day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-Day Recovery
  - 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-Day Recovery
  - H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice
  - 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery
  - H-28548: Combined chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats
  - Oral (Gavage) Reproduction/Developmetal Toxicity Screening Study of H-28548 in Mice
  - Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Benchmark Dose Modeling Progress

- Organization by study:
  - Two data types: continuous and dichotomous
  - Four to eight parameters
  - Organized into tables

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Benchmark Dose Modeling Progress

Parameters (n = 24)

- Body weight
- **Hematology**
- Serum Chemistry
- Macroscopic
- Organ weights
- Microscopic
- Food Consumption
- Clinical Chemistry
- Urinalysis
- Coagulation
- F_0 Body Weights
- F_0 Organ Weights
- F_1 Body Weight
- F_1 Balanopreputial Separation
- F_1 Vaginal Patency
- F_1 Post-Weaning Body Weight
- F_1 Food Consumption
- F_0 Microscopic
- Maternal Body Weight
- Gravid Uterine Weight
- Maternal Macroscopic
- Laparohysterectomy Data
- Maternal Microscopic
- Fetal Morphology

Benchmark Dose Modeling Progress

Endpoints for Hematology Parameter

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Continuous Data (Hematology)

Erythrocyte Count (mil/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	8.8	0.519	
	0.1	8	8.44	0.421	
	3	8	8.28	0.401	
	30	9	8.13	0.447	significant at p=0.05
Females	No significant differences				

Hemoglobin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	14.1	0.53	
	0.1	8	13.8	0.45	
	3	8	13.4	0.46	significant at p=0.05
	30	9	13.1	0.53	significant at p=0.01
Females	No significant differences				

Hematocrit (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	40.1	1.72	
	0.1	8	38.8	1.06	
	3	8	38.1	1.36	significant at p=0.05
	30	9	37.5	1.54	significant at p=0.01
Females	No significant differences				

Differential Leukocyte Count - Monocyte Percent (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	2.4	1.12	
	0.1	8	2.2	0.96	
	3	8	2.6	1.2	
	30	9	4.7	1.63	significant at p=0.01
Females	No significant differences				

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Continuous Data (Hematology)

Differential Leukocyte Count - Large Unstained Cell Percent (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	0.5	0.27	
	0.1	8	0.4	0.22	
	3	8	0.6	0.3	
	30	9	1.3	0.59	significant at p=0.01
Females	No significant differences				

Differential Leukocyte Count - Monocyte Absolute (thous/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	0.1	0.048	
	0.1	8	0.07	0.029	
	3	8	0.12	0.062	
	30	9	0.27	0.146	significant at p=0.01
Females	No significant differences				

Differential Leukocyte Count - Large Unstained Cell Absolute (thous/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	0.02	0.013	
	0.1	8	0.01	0.008	
	3	8	0.04	0.031	
	30	9	0.07	0.055	significant at p=0.01
Females	No significant differences				

Example table – Continuous type data

Study title and data type at the top of each page

Endpoint (and units if applicable) at the top of each table

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery
Continuous Data (Serum Chemistry)

Albumin/Globulin Ratio					
Sex	Dose (mg/kg/day)	N	Mean	St. Dev	Notes
Males	0	10	1.54	0.134	
	0.1	10	1.56	0.128	
	3	10	1.92	0.222	significant at p=0.01
	30	10	2.32	0.241	significant at p=0.01
Females	0	10	1.93	0.159	
	0.1	10	1.98	0.134	
	3	10	2.2	0.087	significant at p=0.01
	30	10	2.46	0.19	significant at p=0.01

Statistical significance noted if analyses provided by study authors

Example table – Dichotomous type data

Study title and data type at the top of each page

Endpoint (and units if applicable) at the top of each table

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery
Dichotomous Data (Microscopic)

Liver Necrosis, Single Cell				
Sex	Dose (mg/kg/day)	N	Incidence (#)	Notes
Males	0	10	0	
	0.1	10	0	
	3	10	4	4 minimal
	30	10	10	10 minimal
Females	0	10	0	
	0.1	10	0	
	3	10	0	
	30	10	4	4 minimal

For histopathology results, severity noted

Benchmark Dose Modeling Requests

N.C. DHHS requests input from the SAB on the following:

1. Review compiled data tables. Provide guidance on the endpoints deemed critical and/or most relevant to human health. These will be the endpoints OEEB will input into BMD software.
2. Provide guidance/justification on benchmark response levels for each endpoint from above. For example, guidance on use of 1 SD change from the mean versus 2 SD (continuous data), 10% or 20% change for dichotomous data. Each endpoint may have a different BMDR.

Benchmark Dose Modeling Next Steps

- OEEB staff will use EPA's BMD software to model selected endpoints at recommended response levels.
- N.C. DHHS will provide the outputs of the model (BMDLs) for SAB consideration and recommendation for use as a point of departure.

Questions?