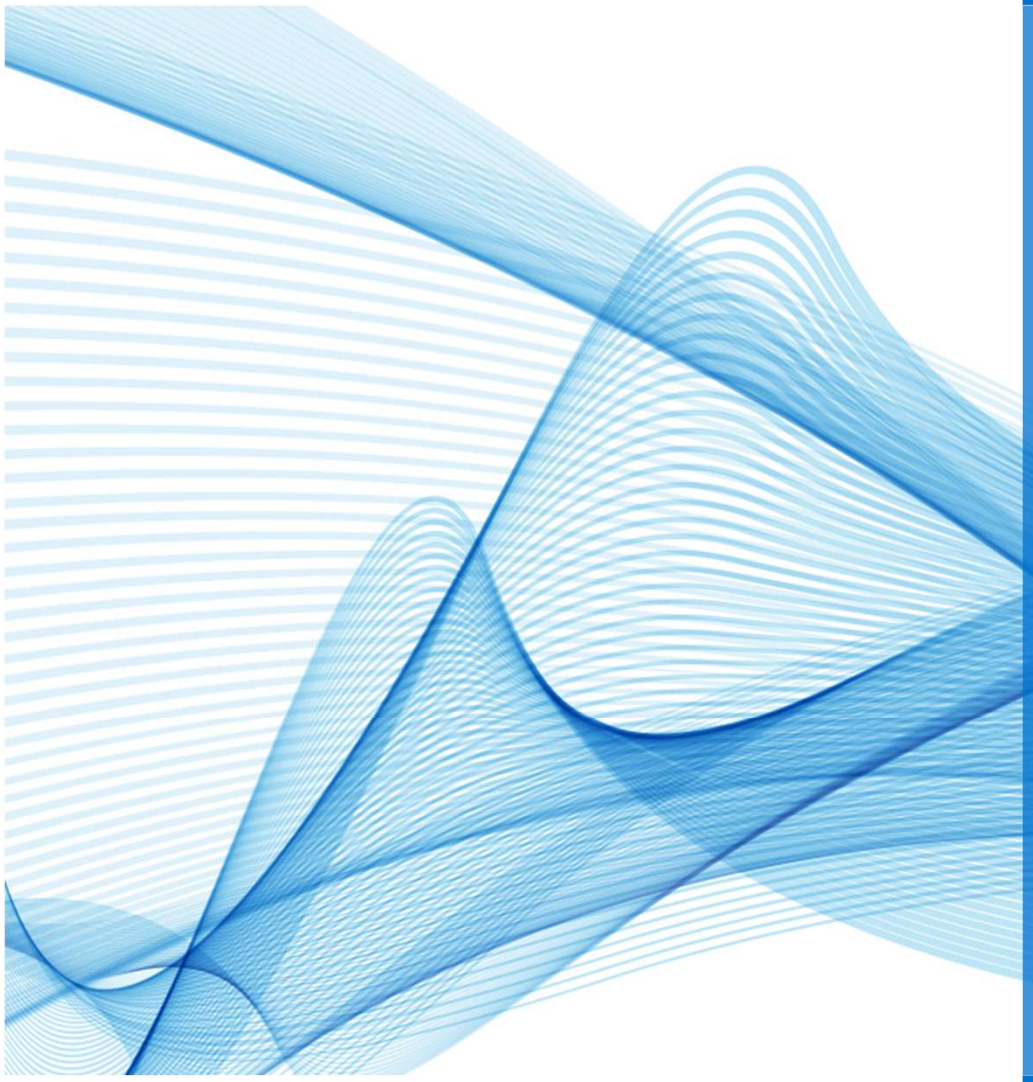

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Evaluation of US EPA's Existing Chemical Exposure Limit (ECEL) for the Occupational Use of Carbon Tetrachloride (CTC)

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Key Points from Gradient's Evaluation of US EPA's 2021 ECEL:

- **US EPA's 2021 ECEL derivation for carbon tetrachloride (CTC) is not consistent with generally accepted scientific approaches** that use state-of-the-science Physiologically-Based Pharmacokinetic (PBPK) and Benchmark Dose (BMD) modeling, including US EPA's own technical and methodological guidance (US EPA, 2005a, 2012, 2022), and its recent IRIS and TSCA CTC evaluations (US EPA 2010, 2020).

- **US EPA's ECEL for CTC (0.03 ppm)** was derived using the more limited and less reliable **LOAEC/NOAEC approach** rather than the preferred BMD modeling approach.

- Using the same data US EPA used, in conjunction with state-of-the-science PBPK and BMD modeling, **Gradient derived a revised ECEL for CTC (1.5 ppm)** that is 50-fold higher than US EPA's proposed ECEL, but below the current OSHA PEL (10 ppm), ACGIH TLV (5 ppm), and NIOSH REL (2 ppm) values.

- **It remains unclear why EPA chose to use the LOAEC/NOAEC approach.** TSCA (Section 26h) requires application of the "Best available science."

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LOAEC = lowest observed adverse effect concentration
NOAEC = no observed adverse effect concentration

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CTC ECEL Does Not Incorporate Best Available Science Previously Supported by EPA (US EPA, IRIS 2010 and TSCA 2020):

- **Physiologically-Based Pharmacokinetic (PBPK) Modeling**
  - Uses internal doses (metabolized CTC) to extrapolate from animals and humans

- **Benchmark Dose (BMD) Modeling** as opposed to Lowest-Observed Adverse Effect Concentration (LOAEC) to derive the Point of Departure (POD)
  - Considers all doses in the study, and
  - Eliminates need for additional uncertainty factors

- **Threshold Mode of Action (MoA) for CTC and Liver Cancer**
  - Evidence supports a nonlinear threshold MoA for CTC-induced liver tumors in rodents, as opposed to a linear low-dose MoA

US EPA has applied all of these for CTC risk evaluations, <u>but not all together</u>

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ECEL Derivation Should Be Based on the Best Available Science

Best Available Science for CTC Cancer Endpoint Includes:	US EPA IRIS 2010	US EPA TSCA 2020/2021	Gradient 2023
Nagano et al. (2007) female mouse liver tumor data (adenomas and carcinomas)	✓	✓	✓
PBPK modeling to estimate CTC internal/metabolized dose in liver	✓	x	✓
BMD modeling to derive POD	✓	x	✓
Threshold MoA for liver tumors	x	✓	✓
Use of appropriate data/methods (*e.g.*, BMD modeling) to eliminate unnecessary uncertainty factors (UFs)	NA	x	✓
Resulting ECEL value	NA	0.03 ppm	1.5 ppm

NA = not applicable; *US EPA IRIS (2010) Toxicological Profile for Carbon Tetrachloride; US EPA TSCA (2020) Risk Evaluation for Carbon Tetrachloride; US EPA TSCA (2021) Existing Chemical Exposure Limit (ECEL) for Occupational Use of Carbon Tetrachloride*

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ECEL Derivation Should Be Based on the Best Available Science

Best Available Science for CTC Cancer Endpoint Includes:	US EPA IRIS 2010	US EPA TSCA 2020/2021	Gradient 2023
Nagano et al. (2007) female mouse liver tumor data (adenomas and carcinomas)	✓	✓	✓
PBPK modeling to estimate CTC internal/metabolized dose in liver	✓	x	✓
BMD modeling to derive POD	✓	x	✓*
Threshold MoA for liver tumors	x	✓	✓
Use of appropriate data/methods (*e.g.*, BMD modeling) to eliminate unnecessary uncertainty factors (UFs)	NA	x	✓
Resulting ECEL value	NA	0.03 ppm	1.5 ppm

Note that our BMD modeling results are statistically valid and identical to EPA's 2010 BMD results

NA = not applicable; *US EPA IRIS (2010) Toxicological Profile for Carbon Tetrachloride; US EPA TSCA (2020) Risk Evaluation for Carbon Tetrachloride; US EPA TSCA (2021) Existing Chemical Exposure Limit (ECEL) for Occupational Use of Carbon Tetrachloride*

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ECEL Derivation Should Be Based on the Best Available Science

Best Available Science for CTC Cancer Endpoint Includes:	US EPA IRIS 2010	US EPA TSCA 2020/2021	Gradient 2023
Nagano et al. (2007) female mouse liver tumor data (adenomas and carcinomas)	✓	✓	
PBPK modeling to estimate CTC internal/metabolized dose in liver	✓	X*	
BMD modeling to derive POD	✓	X*	
Threshold MoA for liver tumors	x	✓	
Use of appropriate data/methods (*e.g.*, BMD modeling) to eliminate unnecessary uncertainty factors (UFs)	NA	x	
Resulting ECEL value	NA	0.03 ppm	1.5 ppm

Note that EPA did apply PBPK and BMD modeling for non-cancer liver effects, and for the adrenal cancer POD, but not for liver tumors

NA = not applicable; *US EPA IRIS (2010) Toxicological Profile for Carbon Tetrachloride; US EPA TSCA (2020) Risk Evaluation for Carbon Tetrachloride; US EPA TSCA (2021) Existing Chemical Exposure Limit (ECEL) for Occupational Use of Carbon Tetrachloride*

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ECEL Derivation Should Be Based on the Best Available Science

Best Available Science for CTC Cancer Endpoint Includes:	US EPA IRIS 2010	US EPA TSCA 2020/2021	Gradient 2023
Nagano et al. (2007) female mouse liver tumor data (adenomas and carcinomas)	✓	✓	✓
PBPK modeling to estimate CTC internal/metabolized dose in liver	✓	x	
BMD modeling to derive POD	✓	x	
Threshold MoA for liver tumors	x	✓*	
Use of appropriate data/methods (*e.g.*, BMD modeling) to eliminate unnecessary uncertainty factors (UFs)	NA	x	
Resulting ECEL value	NA	0.03 ppm	1.5 ppm

Note that EPA used a threshold approach following SACC comments on the 2020 draft that did not consider a threshold

NA = not applicable; *US EPA IRIS (2010) Toxicological Profile for Carbon Tetrachloride; US EPA TSCA (2020) Risk Evaluation for Carbon Tetrachloride; US EPA TSCA (2021) Existing Chemical Exposure Limit (ECEL) for Occupational Use of Carbon Tetrachloride*

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ECEL Derivation Should Be Based on the Best Available Science

Best Available Science for CTC Cancer Endpoint Includes:	US EPA IRIS 2010	US EPA TSCA 2020/2021	Gradient 2023
Nagano et al. (2007) female mouse liver tumor data (adenomas and carcinomas)	✓	✓	✓
PBPK modeling to estimate CTC internal/metabolized dose in liver	✓	x	✓
BMD modeling to derive POD	✓	x	✓
Threshold MoA for liver tumors	x	✓	✓
Use of appropriate data/methods (*e.g.*, BMD modeling) to eliminate unnecessary uncertainty factors (UFs)	NA	x	✓
Resulting ECEL value	NA	0.03 ppm	1.5 ppm

NA = not applicable; *US EPA IRIS (2010) Toxicological Profile for Carbon Tetrachloride; US EPA TSCA (2020) Risk Evaluation for Carbon Tetrachloride; US EPA TSCA (2021) Existing Chemical Exposure Limit (ECEL) for Occupational Use of Carbon Tetrachloride*

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Conclusions

- **It remains unclear why EPA chose to use the LOAEC/NOAEC approach** for determining the POD for the ECEL derivation rather than BMD/PBPK modeling, which are considered more reliable and representative of the current state-of-the-science, and are recommended in its own guidance.

- **It is unclear why EPA used BMD/PBPK modeling in its earlier CTC IRIS 2010 evaluation, and following SACC comments on the 2020 TSCA evaluation, included a threshold MoA, but did not apply the PBPK/BMD modeling it included in 2010.**

- **Had EPA applied the more reliable and scientifically defensible methodologies (PBPK, BMD, and threshold MoA), it would have calculated an ECEL for CTC closer to the ECEL proposed by Gradient (1.5 ppm).**

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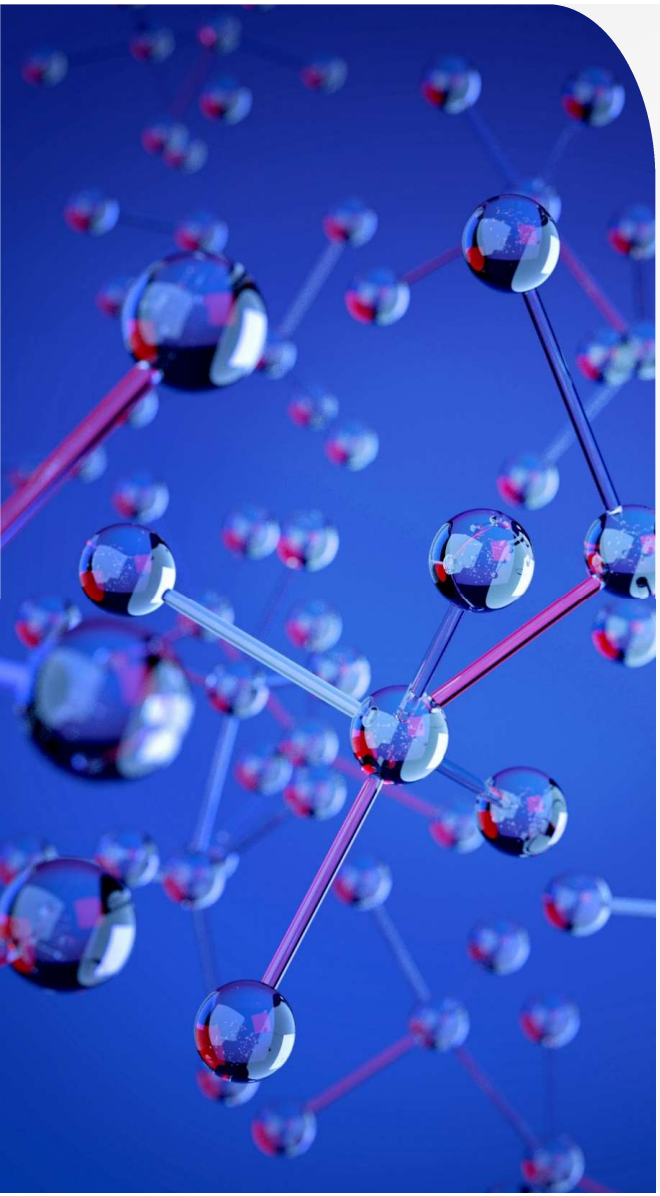
Conditions of Use – Carbon Tetrachloride

- Feedstock for the manufacture of low GWP refrigerants and foam blowing agent
- These products are critical to meeting the objectives of the –
  - American Innovation and Manufacturing (AIM) Act
  - Kigali Amendment to phase down high GWP substances.



Discussion Points

1. Challenge in meeting the ECEL of 0.03 ppm
   a) Technical feasibility to consistently measure for a full work shift below the ECEL.
   b) Technically infeasible to measure short-term e.g., ≤ 1 hour, tasks using current methods.
2. Implementation Schedule:
   a) Time is needed to evaluate the technical feasibility of monitoring methods to measure the CTC ECEL.
   b) Time is needed to conduct an exposure assessment of the ECEL value for different work groups and tasks.
3. Utilize the Exposure Control Plan to demonstrate compliance with the ECEL by allowing:
   a) Incorporation of the Assigned Protection Factor (APF) by task when respirator use is required by the facility Exposure Control Plan.
   b) Use of a rolling 6-sample average.

Supporting Quotes from US EPA Guidance & Other References

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US EPA Prefers BMD Modeling to the LOAEC/NOAEC Approach

- **US EPA, IRIS Toxicological Review of Carbon Tetrachloride (2010):**
  - "A NOAEL or LOAEL lacks characterization of the dose-response curve, and for this reason, is less informative than a POD obtained from BMD modeling" (p. 213).

- **US EPA, Benchmark Dose Technical Guidance (2012):**
  - "The BMD approach can be used to implement the recommendations in U.S. EPA's 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA 2005a) regarding modeling tumor data" (p. 6).
  - "Unlike NOAELs and LOAELs, the BMD and BMDL are not constrained to be one of the experimental doses, and the BMDL can thus be used as a more consistent and better defined POD …" (p. 7).
  - "Because of the limitations of the NOAEL/LOAEL approach…, the BMD approach is preferred to the NOAEL/LOAEL approach" (p. 6).
  - "…the application of BMD methods…has an inherent advantage over the use of a NOAEL or LOAEL by making greater use of all the data from the study" (p. 211).

- **US EPA, Risk Evaluation for Carbon Tetrachloride (2020):**
  - "Benchmark dose modeling is the preferred method used in human health fields to predicting toxicity effect values for a given endpoint and study" (p. 339).

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US EPA Prefers BMD Modeling to the LOAEC/NOAEC Approach

- **US EPA, Benchmark Dose Software Version 3.3 User Guide (2022):**
  - "Prior to the availability of tools such as BMDS, noncancer risk assessment benchmarks such as RfDs and RfCs were determined from no-observed-adverse-effect levels (NOAELs)…however, using the NOAEL in determining RfDs and RfCs has long been recognized as having limitations" (p. 12).
  - "A goal of the BMD approach is to define a starting point of departure (POD) for the computation of a reference value (RfD or RfC) or slope factor that is more independent of study design" (p. 13).

- **US EPA, Benchmark Dose Training Video (2022)[a]:**
  - "The BMDL is the preferred point of departure in IRIS for our human health risk assessments."
  - "The BMD approach was developed as a method to address well-known limitations in the NOAEL approach."
  - "The BMD approach addresses these limitations and is a methodological improvement over the NOAEL/LOAEL approach."

a) Narrated by J. Allen Davis, MSPH, US EPA, Center for Public Health and Environmental Assessment (CPHEA)

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BMD Modeling *vs.* LOAEC/NOAEC Approach (US EPA, 2022)

Subject	LOAEC/NOAEC Approach	BMD Approach
Dose Selection	**LOAEC/NOAEC are limited to study doses**	**BMD and BMDL are not constrained**
Sample Size	Highly dependent on sample size: ↓ N = ↑ NOAEC	Appropriately considers sample size: ↓ N = ↓ BMDL
Cross-Study Comparison	Response levels cannot be compared across studies	Response levels (BMRs) are comparable across studies
Variability and Uncertainty in Experimental Results	Dose selection and sample size not fully considered	Dose selection and sample size are considered
Dose-Response Information	Dose-response curve shape is not considered	Full dose-response curve is considered
NOAEL Not Identified in Study	**LOAEC-to-NOAEC uncertainty factor is necessary**	**BMDL ≈ NOAEC** **No uncertainty factor necessary**

Adapted from "Introduction to Benchmark Dose Modeling", US EPA, 2022

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US EPA Recommends Use of CTC PBPK Model for Liver Effects

- **US EPA, IRIS Toxicological Review of Carbon Tetrachloride (2010):**
  - "PBPK modeling is considered to reduce the uncertainty in extrapolating rodent tumor data to humans" (p. 252).
  - "Availability of an inhalation PBPK model generally reduces the toxicokinetic component of uncertainty associated with animal to human extrapolation by moving away from default assumptions" (p. 214).
  - "Internal dose metrics were selected that were considered to be most relevant to the toxicity endpoints of interest (*i.e.*, liver tumors and pheochromocytomas), based on consideration of evidence for MOA of [CTC]" (p. 230).
  - "Liver metabolism rate [time-averaged rate of metabolism of carbon tetrachloride (MRAMKL, µmol/hr/kg liver)] was selected as the primary dose metric for liver effects based on evidence that metabolism of carbon tetrachloride *via* CYP2E1 to highly reactive free radical metabolites plays a crucial role in its MOA in producing liver toxicity" (p. 230).

- **US EPA, Risk Evaluation for Carbon Tetrachloride (2020):**
  - "The metabolism of carbon tetrachloride to trichloromethyl and trichloromethyl peroxy radicals is an obligatory step in carbon tetrachloride's MOA" (p. 363).
  - "Because the MOA for carbon tetrachloride-induced hepatotoxicity involves metabolism to reactive metabolites in the liver, HECs based on the mean rate of metabolism in the liver (MRAMKL) dose metric is the most proximate to the critical effect" (p. 160).

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US EPA Supports a Nonlinear Threshold Mode of Action for CTC and Liver Tumors

- **US EPA, IRIS Toxicological Review of Carbon Tetrachloride (2010):**
  - "The available data for carbon tetrachloride provide scientific support for a MOA for liver tumors involving metabolism to reactive intermediates, hepatocellular toxicity, and sustained regenerative and proliferative changes that is consistent with a nonlinear extrapolation approach" (p. 223).
  - "This potential MOA has been extensively investigated, and appears to be a major factor driving the steep nonlinear increase in liver tumor dose-response at relatively high carbon tetrachloride exposures" (p. 166).
  - "Under this hypothesized MOA, liver carcinogenicity occurs at carbon tetrachloride exposures that also induce hepatocellular toxicity and a sustained regenerative and proliferative response; exposures that do not cause hepatotoxicity are not expected to result in liver cancer" (p. 261).
  - "For this hypothesized MOA for carbon tetrachloride liver carcinogenicity, a nonlinear approach to low-dose extrapolation may be considered appropriate" (p. 247).

- **US EPA, Risk Evaluation for Carbon Tetrachloride (2020):**
  - "Based on reasonably available data, regenerative hyperplasia is the cancer MOA identified for the development [of] liver tumors in animals exposed to high doses of carbon tetrachloride. Therefore, a threshold cancer risk model was used to calculate risks for liver tumors" (p. 23).

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Peer Reviewers Support Use of a Threshold Mode of Action (MoA)[1]

- Recommendation 55: Consider adoption of a threshold-type MOA in estimating the carcinogenic risks of carbon tetrachloride
  - "No support is provided for EPA's designation of an 'alternate MOA' that combines cytotoxic mechanisms at relatively high CCl4 doses with 'alternate, non-cytotoxic mechanisms' at lower doses."
  - "Most of the Committee members recommended that the EPA consider adoption and implementation of a threshold MOA when estimating cancer risks."

[1] Final Report for the TSCA Science Advisory Committee on Chemicals Carbon Tetrachloride Meeting held February 25-26, 2020.

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Recent Article by Cohen *et al.* (2023) Supports a Nonlinear Threshold Mode of Action for CTC and Liver Tumors

- **"** The important component of [the CTC] MOA is the induction of cell injury to a level sufficient to produce cell death (necrosis) that results in consequent hepatocyte cell proliferation. The insult must be chronic. Doses or exposures that do not induce sufficient cytotoxicity to elicit compensatory hyperplasia do not start the cascade to neoplasm formation. Alternative MOAs, including genotoxicity, have been excluded" (p. 15).
- "There is a good correlation (particularly at higher exposures, *i.e.*, > 5 ppm by inhalation) between occurrence of hepatotoxicity and/or regenerative/proliferative lesions and development of tumors (Nagano *et al.*, 2007a; 2007b)" (p. 15).
- "Liver tumors in rats were observed at an exposure level associated with hepatotoxicity following subchronic and chronic exposure; tumors were not observed at an exposure level below the level that induced cytotoxicity (< 10 ppm for 13-week exposure and 5 ppm for 104-week exposure)" (p. 19).

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Additional Slides

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ECEL Derivation using the LOAEC/NOAEC Approach *vs.* BMD & PBPK Approach

Approach Variables	US EPA 2021 ECEL Derivation	Gradient 2023 ECEL Derivation
Study	Nagano *et al.* (2007)	Nagano *et al.* (2007)
Data	Female mouse liver tumor data	Female mouse liver tumor data
Overall Approach	LOAEC/NOAEC Approach	BMD Modeling Approach[a]
Use of PBPK Modeling	No	Yes
POD (value), continuous human exposure	LOAEC (6 mg/m^3)	$BMDL_{10[HEC]}$ (32.8 mg/m^3)[b]
Uncertainty Factor	300	30[c]
Continuous exposure concentration	0.02 mg/m^3	1.09 mg/m^3
Final ECEL (occupational exposure)	0.03 ppm	50-fold	1.5 ppm

a) Model fits are statistically valid and identical to EPA's 2010 BMD results; b) Value is very close to EPA's 2010 value; c) No LOAEC-to-NOAEC uncertainty factor is necessary when using BMD modeling (BMDL ≈ NOAEC); c) Presumed to be submitted to OMB by EPA in 2023.

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