Table 1. Summary of Agency Toxicity Assessments Conducted Previously for BD

Assessor (Year)	Assessment	Endpoint	Data set	Toxicity Value	Limitations
Health Canada (2000)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	LEC05 = 0.44 mg/m^3 (200 ppb)	Interspecies extrapolation approach does not reflect current understanding
	Cancer	Leukemia	SBR workers (Delzell et al. 1995)	TC01 = 1.7 mg/m^3 (770 ppb)	Cohort and exposures are not current
USEPA (2002)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	RfCc = 0.9 ppb	Interspecies extrapolation approach does not reflect current understanding
	Acute & Subchronic Noncancer	Fetal body weight	Mice (Hackett et al. 1987a)	RfCs = 7 ppb	Interspecies extrapolation approach does not reflect current understanding
	Cancer	Leukemia	SBR workers (Delzell et al. 1995)	0.08 (per ppm)	Cohort and exposures are not current
ATSDR (2012)	Acute, Intermediate, Chronic Minimal Risk Levels (MRLs)	ATSDR elected to not derive acute-, intermediate-, and chronic-duration inhalation minimal risk levels for BD due to the lack of chemical-specific data to adjust for the large species differences in metabolism, which may result in the MRL overestimating the risk to humans			
OEHHA (2013)	Acute Reference Exposure Level (REL)	Fetal body weight	Mice (Hackett et al., 1987a; as reanalyzed by Green, 2003)	297 ppb	Interspecies extrapolation approach does not reflect current understanding
	8-Hours REL	Ovarian atrophy	Female mice (NTP, 1993; Doerr et al., 1996)	4 ppb	Interspecies extrapolation approach does not reflect current understanding
	Chronic REL	Ovarian atrophy	Female mice (NTP, 1993)	1 ppb	Interspecies extrapolation approach does not reflect current understanding
	Inhalation unit risk (NSRL basis)	Multiple tumors	Mice (NTP, 1984; Melnick et al. 1990)	0.00017 (per ug/m3) (0.00038 per ppb)	Interspecies extrapolation approach does not reflect current understanding
TCEQ (2015)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	15 ppb	Interspecies extrapolation approach does not reflect current understanding

	Acute Noncancer	Fetal body weight	Mice (Hackett et al. 1987a)	430 ppb (24-hr)	Interspecies extrapolation approach does not reflect current understanding
	Chronic cancer inhalation unit risk	Leukemia	SBR workers (Sathiakumar and Delzell, 2009)	5.0E-07 per µg/m3 (1.1E-06 per ppb)	Cohort is not current

Table 2. Science Advisory Panel for BD Risk Assessment

Name	Country	Employment Sector	Advanced Degree	Years Post-Degree	Publications	Areas of expertise
Dr. Gunnar Boysen	United States	Academia	PhD	22	85	Biomarkers (including those for BD), biomonitoring, exposure assessment, carcinogenic pathways
Dr. Igor Burstyn	United States	Academia	PhD	23	216	Exposure assessment, occupational epidemiology, statistical methods in occupational hygiene, occupational exposure limits, risk assessment
Dr. Michael DiNovi	United States	Consulting (former government)	PhD	42	92	Risk assessment, exposure assessment, food chemicals
Dr. Robert Roy	United States	Consulting (former industry)	PhD	35	29	Occupational exposure limits, occupational health risk assessment
Dr. Rita Schoeny	United States	Consulting (former government)	PhD	47	97	Human health risk assessment, regulatory toxicology, exposure assessment, mixtures, carcinogenicity, biomarkers
Dr. Babasaheb Sonawane	United States	Consulting (former government)	PhD	53	137	Developmental and reproductive toxicology, regulatory toxicology
Ms. Linda Teuschler	United States	Consulting (former government)	MS	37	68	Quantitative human health risk assessment, mixtures, dose-response modeling, Monte Carlo simulations, statistics
	Total: US (7)	***Academia (2); Consulting, former government (4); Consulting, former industry (1)***	***PhD (6); MS (1)***	***259***	***724***	

Table 3. Summary of Key Input from Independent Science Advisory Panel for the Quantitative Human Health Risk Assessment (see Appendix B for complete charge questions, panel responses, and comments)

Charge Question	Panel Response	Notes
1.1: As summarized review material, based on a consideration of BD's emissions (>99% to air), physical chemical properties (e.g., boiling point of -4.5 degrees C), and toxicity database (almost exclusively via the inhalation pathway), a decision was made to focus efforts for the quantitative risk assessment on the inhalation pathway. Do you agree with this decision? Please explain your answer.	All 7 experts agreed with focusing on the inhalation pathway; Key reasons: >99% of emissions are to air, physical/chemical properties, toxicity database almost exclusively via inhalation	Some experts suggested other routes should still be discussed qualitatively; One expert recommended quantitatively assessing other routes if feasible, to pre-empt potential questions
1.2: For assessing inhalation exposures to BD, please provide your recommendation for including the following points of exposure in the quantitative risk assessment: Workplace Air, Ambient Air, Indoor Air (e.g., residence, office), In-vehicle air, Other (please explain)	Workplace Air: All 7 experts recommended including in quantitative assessment; Ambient Air: All 7 experts recommended including in quantitative assessment; Indoor Air: 6/7 experts recommended quantitative assessment; In-vehicle Air: 5/7 experts recommended quantitative	Several experts emphasized the importance of considering smoking as a major non-occupational source; - Some debate on whether indoor/in-vehicle exposures warrant quantitative assessment given limited data; - Suggestion to consider climate change impacts on wildfire-related exposures
1.3: As summarized in review material, a number of other exposure pathways are considered to be either negligible (relative to inhalation) or incomplete. Please provide your recommendation for considering additional exposure pathways in the risk assessment: Dermal contact with liquid BD solutions (workers), Ingestion of groundwater, Ingestion in the diet from food contact materials, Ingestion from consumer products (e.g., gum, mouthing of toys), Other (please explain)	Dermal contact (workers): All 7 experts said exclude from quantitative assessment groundwater: 5/7 said to exclude; Ingestion from food contact: 6/7 said to exclude Ingestion from consumer products: 6 said exclude, 1 other	General agreement these pathways are likely negligible compared to inhalation; - Some experts suggested quantitatively showing these are insignificant if data available; - Recommendation to qualitatively discuss frostbite hazard from liquid 1,3-BD contact

1.4: Please provide your recommendation for considering human health receptors in the risk assessment for BD.	BD manufacture workers: All 7 experts said include in quantitative assessment; - Downstream workers: All 7 experts said include in quantitative assessment; General public: 5/7 said quantitative	Suggestion to give special consideration to smokers' households and second-hand smoke exposure; - Recommendation to evaluate professional drivers as potentially highly exposed group; - Debate on whether general population exposure data is adequate for quantitative assessment; - Some experts emphasized need to consider all life stages and susceptible subpopulations
2.1: Please provide your recommendation for including the following noncancer endpoints in the quantitative risk assessment.	Fetal body weight changes: 5/7 said include in quantitative assessment Ovarian atrophy: 5/7 said include in quantitative	General agreement on including these endpoints, but some debate on relevance to humans; - Suggestion for comprehensive literature review to identify any new relevant endpoints; - Recommendation to consider species differences in metabolism and toxicokinetics; - Need for clear articulation of human relevance for rodent endpoints
2.2: Please provide your recommendation for including the following cancer potency datasets in the quantitative risk assessment.	Mortality data from epidemiology: All 7 experts said include in quantitative assessment; Cancer incidence from rodent bioassays: 4/7 said include in quantitative	Strong preference for using human epidemiological data (SBR cohort); Debate on the relevance and inclusion of rodent bioassay data; Suggestion to consider confounding factors (e.g., smoking, co-exposure to styrene); Recommendation for independent expert review of epidemiological studies; Need to address species differences in metabolism and potential non-linearity in dose-response
3.5: In Table 2-3, the published data of Scarselli et al. (2017) for Italian workers are proposed as a potential surrogate for U.S. worker exposures. Do you consider this use of the data appropriate. Please explain your answer.	Mixed responses: 3/7 Yes; 1/7 No; 2/7 Cannot answer	Concerns about differences in regulations and practices between Italy and the US; - Suggestion to use Scarselli data to supplement, not replace, SBR worker data; - Concerns about concurrent exposures to other chemicals in the Scarselli data
4.1: Based upon input received from the panel during Round 1, there is a clear preference for relying on epidemiology data to support the calculation of an inhalation unit risk value. Which data sets should be used to support this calculation?	All 7 experts selected SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)	General agreement on using the most recent and comprehensive dataset; - Valdez-Flores et al. (2022) approach seen as reasonable; - Includes both male and female workers, improved BD exposure estimates, and more outcome data
4.2: Using the epidemiology data, what endpoint(s) should be used to calculate the inhalation unit risk?	Mixed responses:; 3/7 for Aggregate (Leukemia + Bladder cancer); 1/7 for Leukemia; 2/7 for Other (consider both separately	Some experts suggest analyzing both endpoints separately and together; - Debate on whether to combine endpoints or keep them separate; - Suggestion to present plausible alternatives with pros and cons

	and together); 1/7 Cannot answer	
4.3: Within the Cox proportional hazards modeling (e.g., Valdez-Flores et al. 2022), what covariates should be included in the regression model used to calculate the inhalation unit risk?	Mixed responses: 3/7 for Only statistically significant covariates; - 1/7 for Other; 3/7 Cannot answer	Debate on using statistical significance for covariate selection; Suggestion to use directed acyclic graphs (DAG) for covariate selection; - Discussion on the importance of testing proportional hazards assumption; Consideration of both non-exposure and exposure variables
5.1: Please indicate your preference for adjusting for species differences when extrapolating fetal body weight dose-response data from rodents to humans	5/7 experts selected:; Internal dose based on metabolite-specific hemoglobin adducts	Agreement on the importance of accounting for species differences in metabolic activation; Support for using hemoglobin adduct data to address species differences; Suggestion to include free oxides in blood and urine biomarker studies as supporting evidence
5.2: As discussed in Kirman et al. (2022), species differences are noted for fetal body weights changes as reported in mice and rats exposed to BD (Hackett et al. 1987a,b), which may be explained by species differences in metabolic activation of BD. Please indicate your preference on the species used to support toxicity values for BD human health risk assessment	3/7 experts selected mouse data; 1/7 expert selected rat data; 1/7 expert selected data from both species; 2/7 experts could not answer	Mouse data shows effects at all tested concentrations, while rat data shows no clear dose-response; Suggestion to use combined dataset to increase confidence in extrapolation to humans; Discussion on metabolic differences between species
5.7: The study of Hackett et al. (1987) included exposures to rodents for a substantial fraction of rodent gestation (GD6-15 of a 21-day gestation period). For methods based on best available science, to what exposure duration in humans should these data be compared in order to maintain exposure duration concordance across the exposure assessment and toxicity assessment components of the risk assessment.	3/7 experts selected full human 40-week gestation period; 1/7 expert selected a defined fraction of human gestation (50%); 3/7 experts could not answer	Support for extrapolating rodent data to full human gestation period; Discussion on the appropriateness of using standard developmental toxicity testing protocols
6.1: As discussed in Kirman et al. (2022), species differences are noted for ovarian atrophy reported in mice and rats exposed to BD, which may be explained by species differences in metabolic activation of BD. Please indicate your preference on the species used to support toxicity values for BD human health risk assessment.	Mixed responses: 2/7 for mouse data; 1/7 for rat data; 2/7 for data from both species	Mouse data shows effects at all tested concentrations, while rat data shows no clear dose-response; Suggestion to use combined dataset to increase confidence in extrapolation to humans; - Discussion on metabolic differences between species

6.3: Please indicate your preference for adjusting for species differences when extrapolating ovarian atrophy dose-response data from rodents to humans	5/7 experts selected: Internal dose based on metabolite-specific hemoglobin adducts	Agreement on the importance of accounting for species differences in metabolic activation; Support for using hemoglobin adduct data to address species differences
7.5: Should the hemoglobin adduct data for butadiene metabolites in exposed workers (Section 4 of the Round 5 Summary Report) be used to quantify human variation in toxicokinetics for use in uncertainty factor and margin of exposure determination?	Majority: 5/7 Yes	Support for using Hb adduct data to determine kinetic portion of UFh; - Suggestion to use data-derived extrapolation factors; - Discussion on combining data from males and females

Table 4. Proposed Exposure Pathways for Human Health Risk Assessment of BD

Life Cycle Stage / Exposure Category	Receptor	Exposure Scenario(s)	Exposure Media	Exposure Route	Evaluation in Risk Assessment	Rationale for Further Evaluation / no Further Evaluation
Manufacture	Manufacturing Workers	- Instrument and Electrical - Laboratory Technician - Machinery and Specialists Group - Maintenance - Operations Onsite - Safety Health and Engineering - Missing Job Group Designation - Occupational Non-User	Workplace Air	Inhalation	Yes (quantitative)	Comprehensive IH data available (**Table 4**; Panko et al. 2023). The effect of PPE on exposure estimates should be considered.
				Dermal vapor	No	The dermal absorption of BD vapor is expected to be orders of magnitude lower than corresponding inhalation exposures. The dermal vapor pathway has not been explicitly assessed for worker exposures used to characterized BD cancer and noncancer potency.
			Liquid	Dermal contact	No	Due to engineering controls and use of PPE, dermal exposures are not expected to occur. Due to physical-chemical properties (e.g., boiling point of -4.5 C), rate of volatilization from skin is expected to far exceed rate of absorption. The dermal vapor pathway has been ignored for the worker exposures used to characterized BD cancer and noncancer potency.
Industrial Use	SBR Workers	- Analyze samples - Collect samples - Connecting/Disconnecting - Maintenance Jobs - Routine Rounds	Workplace Air	Inhalation	Yes (quantitative)	Limited IH data are available for SBR workers (**Table 3**; IISRP, 2020). The effect of PPE on exposure estimates should be considered.
				Dermal vapor	No	The dermal absorption of BD vapor is expected to be orders of magnitude lower than corresponding inhalation exposures. The dermal vapor pathway has not been explicitly assessed for worker exposures used to characterized BD cancer and noncancer potency.
			Liquid	Dermal contact	No	Due to engineering controls and use of PPE, dermal exposures are not expected to occur. Due to physical-chemical properties (e.g., boiling point of -4.5 C), rate of volatilization from skin is expected to far exceed rate of absorption. The dermal liquid pathway has been ignored for the worker exposures used to characterized BD cancer and noncancer potency.

	Other Downstream Users	From USEPA (2020a): Adhesives and Sealants (epoxy resins) Automotive Care Products Fuel and Related Products Laboratory Chemicals Paints and Coatings Processing aids specific to petroleum production (e.g. hydraulic fracturing fluid)	Workplace Air	Inhalation	Yes (quantitative)	Occupational exposures to BD for a wide variety of job categories have been characterized in Italy (Scarselli et al. 2017).
				Dermal vapor	No	The dermal absorption of BD vapor is expected to be orders of magnitude lower than corresponding inhalation exposures. The dermal vapor pathway has not been explicitly assessed for worker exposures used to characterized BD cancer and noncancer potency.
			Liquid	Dermal contact	No	Due to engineering controls and use of PPE, dermal exposures are not expected to occur. Due to physical-chemical properties (e.g., boiling point of -4.5 C), rate of volatilization from skin is expected to far exceed rate of absorption. The dermal liquid pathway has been ignored for the worker exposures used to characterized BD cancer and noncancer potency.
Offsite Release from Facilities	General Public	General Public	Ambient Air	Inhalation	Yes (quantitative)	Ambient air monitoring (USEPA, 2020d) and air modeling data near industrial facilities are available (AECOM, 2024); Contributions from nonindustrial releases are important and should also be considered
Consumer Products			Consumer Goods/Food Packaging	Ingestion	No	Levels of residual monomer in consumer goods (plastic, rubber products) are either low or below limits of detection. Detectable levels do not migrate and therefore are not considered to be bioavailable (see **Table 6**). Agencies have historically considered non-inhalation pathways to be negligible (see Section 2.6)
Other Sources			Indoor Air	Inhalation	Yes (quantitative)	Publications on indoor air levels of BD are available (reviewed in Huy et al., 2018; Logue et al. 2011)
			In-vehicle Air	Inhalation	Yes (quantitative)	Publications on in-vehicle air levels of BD are available (reviewed in Huy et al., 2018)
			Smoking	Inhalation	Yes (semi-quantitative)	Biomonitoring data for the U.S. population can be used to make relative comparisons between smokers and nonsmokers (Nieto et al. 2021)

Shaded regions indicate exposure pathways that are considered to be incomplete or negligible.

Table 5. Exposure Scenarios Considered in the Quantitative Human Health Risk Assessment

Scenario	Group (Reference)	Worker	Exposure Media	Exposure Scenario Variations
W1	BD Manufacture Workers (Panko et al., 2023)	Infrastructure/Distribution Operations	Workplace air	4 levels of respiratory protection 1) Half-mask respirator 2) Full-mask respirator 3) Supplied air respirator 4) None
W2		Instrument and Electrical		
W3		Laboratory Technician		
W4		Machinery and Specialists Group		
W5		Maintenance		
W6		Operations Onsite		
W7		Safety Health and Engineering		
W8		Missing Job Group Designation		
W9		Occupational Non-User		
W10	SBR Workers (IISRP, 2020)	Analyze Samples		
W11		Collect samples		
W12		Connecting/ Disconnecting		
W13		Maintenance Jobs		
W14		Routine Rounds		
W15	Tire Manufacture Workers (TMA, 2020)	Workers		
W16		Occupational Non-User		
W17	All other worker categories (Scarselli et al., 2017)	High exposure: Petroleum- and natural-gas-refining-plant operators 1		
W18		Medium: Petroleum- and natural-gas-refining-plant operators 2		
W19		Low: Plastic-products machine operators		
A1	Aggregate Exposures	General Population (nonsmoker)	Ambient air (US average), indoor air, in-vehicle air	NA
A2		General Population (nonsmoker)	Ambient air (TX average), indoor air, in-vehicle air	
A3		General Population (nonsmoker)	Ambient air (Houston average, measured), indoor air, in-vehicle air	

A4		General Population (nonsmoker)	Ambient air (Houston average, modeled), indoor air, in-vehicle air	4 distance categories: 1) Fenceline, 2) Near, 3) Mid, 4) Far
A5		General Population (A3) + Worker (W7)	Ambient air (Houston average, measured), indoor air, in-vehicle air, workplace air	NA
A6		General Population (A3) + Smoking	Ambient air (Houston average, measured), indoor air, in-vehicle air, smoking	NA
A7		General Population (A3) + Worker (W7) + Smoking	Ambient air (Houston average, measured), indoor air, in-vehicle air, workplace air, smoking	NA

NA=not applicable

Table 6. Exposure Parameter Assumptions for Worker Scenarios

Scenario Group	Parameter (abbreviation)	Units	Value/Distribution	Basis/Rationale
BD Manufacture Worker Scenarios	Air concentration (Ca)	ppm	Scenario-specific normal distributions	Distributions based on the Kaplan-Meier mean and SEM values for BD manufacture workers (Panko et al., 2023, Table 2-1 in Appendix A). Distributions reflect temporal and inter-individual variation in the air concentration for long-term exposures to BD
SBR Worker Scenarios	Air concentration (Ca)	ppm	Scenario-specific normal distributions	Distributions based on the summary statistics for SBR workers (IISRP, 2020; Table 2-2 in Appendix A). Distributions reflect temporal and inter-individual variation in the air concentration for long-term exposures to BD
Tire Manufacture Worker Scenarios	Air concentration (Ca)	ppm	Scenario-specific normal distributions	Distributions based on the summary statistics for tire workers (TMA, 2020; Table 2-3 in Appendix A). Distributions reflect temporal and inter-individual variation in the air concentration for repeated exposures to BD
All Other Worker Scenarios	Air concentration (Ca)	ppm	Scenario-specific normal distributions	Distributions based on the summary statistics for a wide variety of workers (Scarselli et al., 2017; Table 2-4 in Appendix A). Distributions reflect temporal and inter-individual variation in the air concentration for repeated exposures to BD
All worker scenarios	Breathing rate ratio (BR)	Unitless	Uniform(1,2)	Distribution based on professional judgement to consider the possibility that the chronic and subchronic average inhalation rate in worker populations may be higher than the average values used in the toxicity assessments. Distribution intended to account for inter-individual variation.
	Exposure Duration (ED)	Years	Chronic: Pert(1, 7.9, 45)	A mean of 7.9 years for occupational tenure is based on USEPA (2011), with a range from 1 year to 45 years defined based on professional judgment. This distribution reflects inter-individual variation.
	Exposure Frequency (EF)	Days/ year	Pert(150, 240, 300)	A default value of 240 days/year was adopted for central tendency. For purposes of characterizing variation in this term, a range of 150-300 days/year was assumed based on professional judgement. This distribution reflects inter-individual variation.
	Exposure Time (ET)	Hours/day	Pert(6,8,12)	A default value of 8 hours for ET for workers was adopted for central tendency. For purposes of characterizing variation in these terms, a range of 6-12 hours/day was adopted based on professional judgment. This distribution reflects inter-individual variation.

	Protection Factor 1 (PF1)	Unitless	Lognormal(3.79,0.84)	Based on three papers that specifically characterize variation in WPF values specifically for vapor exposures (Cohen et al. 1984; Galvin et al. 1990; Weber and Mullins, 2000) (see Figure 3-3, **Appendix A**).
	Protection Factor 2 (PF2)	Unitless	5x(Protection Factor 1)	Calculated from Protection Factor 1.
	Protection Factor 3 (PF3)	Unitless	Custom cumulative distribution	Based on the data from Cohen et al. (2001) (see Table 3-5, **Appendix A**).
	Exposure Frequency, workplace air	Days/Year	Pert(150,240,300)	Based on professional judgement
	Exposure Time, workplace air (ETw)	Hours/day	Pert(6,8,12)	Based on professional judgement
	Lifetime	Years	Point(78)	Average life expectancy for men and women in the US (USEPA, 2011)

Table 7. Exposure Parameter Assumptions for General Population Aggregate Scenarios

Parameter (abbreviation)	Units	Value/Distribution	Basis/Rationale
Ambient air concentration (Ca)	ppm	Scenario-specific normal distributions: 1) US: Normal(0.000058, 0.000012) 2) Texas: Normal(0.000057, 0.000023) 3) Houston, measured: Normal(0.000080, 0.0000038) 4) Houston, modeled for four distance categories: • Fenceline • Near • Mid • Far	1) US: 24-hour average concentration of BD based upon air monitoring locations across the U.S. in 2020 (reflects multiple sources)(USEPA, 2020). Distribution reflects temporal and spatial variation in the air concentration for long-term exposures to BD 2) Texas: 24-hour average concentration of BD based upon air monitoring locations across Texas in 2020 (reflects multiple sources)(USEPA, 2020d). Distribution reflects temporal and spatial variation in the air concentration for long-term exposures to BD 3) Houston: 24-hour average concentration of BD based upon air monitoring data for station HRM-16 near a BD facility in Houston, TX in 2021 (reflects multiple sources) (AECOM, 2024). Distribution reflects temporal variation in the air concentration for long-term exposures to BD 4) Houston: 24-hour average concentration of BD based upon air modeling predictions near BD facility in Houston, TX (reflects site-related releases) (AECOM, 2024). Distribution reflects spatial variation in the air concentration for longterm exposures to BD.
Indoor air concentration	ppm	Normal(0.00021,0.000074)	Distribution reflects the distribution concentrations based on 879 samples for BD considered to be representative of U.S. residences summarized by Logue et al (2011). This value reflects both inter-individual and temporal variation.
In-vehicle air concentration	ppm	Pert(0.00014,0.00075,0.017)	Distribution reflects the range of concentrations as reviewed and summarized buy Huy et al (2018). This value reflects both inter-individual and temporal variation.
Breathing rate ratio	Unitless	Chronic: Point(1) Subchronic: Uniform(1,2)	For chronic scenarios, this term was set to a value of 1. For subchronic scenarios, a distribution was adopted based on professional to allow for higher inhalation rates during pregnancy

			(Table 2-8, Appendix A). This distribution reflects inter-individual variation.
Lifetime	Years	Point(78)	Average life expectancy for men and women in the US (USEPA, 2011)
Exposure Frequency, ambient and indoor air (EF)	Days/year	Pert(300,350,365)	A default value of 350 days/year was adopted for central tendency. For purposes of characterizing variation in this term,a range of 300-365 days/year was assumed based on professional judgement. This distribution reflects inter-individual variation.
Exposure Frequency, in-vehicle air	Days/Year	Pert(50,250,365)	Based on professional judgement
Exposure Frequency, in-vehicle air	Days/Year	Pert(50,250,365)	Based on professional judgement
Exposure Time, ambient air (ETa)	Hours/day	Pert(0,4.3,8.5)	Based on time spent outdoors (USEPA, 2011; see Table 2-10 in Appendix A)
Exposure Time, in-vehicle air (ETiv)	Hours/day	Normal(1.6,0.02)	Based on mean and SEM for time spent in vehicles (USEPA, 2011; see Table 2-11 in Appendix A)
Exposure Time, Indoor air (ETia)	Hours/day	Calculated	Calculated as 24 hours less time spent outdoors, in vehicles, and at work
BD Biomarker (4HeBMA) in US Smokers	ug/L	Normal(35.4,0.95)	Based upon the mean and SEM for the US population (NHANES; see Figure 1)
BD Biomarker (4HEBMA) in US Nonsmokers	ug/L	Normal(5.6,0.069)	Based upon the mean and SEM for the US population (NHANES; see Figure 1)

Table 8. Toxicity Parameter Assumptions

Hazard Assessment	Parameter	Endpoint	Point of Departure (POD) or Inhalation Unit Risk (IUR)	Distribution	Additional Calculations
Noncancer	Subchronic POD	Fetal body weight changes (Hackett et al., 1987a)	Key POD was defined as the human equivalent concentration (adjusted for species differences in the internal dose of BD metabolites) corresponding to a body weight change of 1 standard deviation in unexposed animals (BMD1SD) based on mouse data (Hackett et al., 1987a)	Custom distribution based on BMDS output that reflects uncertainty in model parameters (ppm): Min = 1443 Max = 5197 5th% = 1716 10th% = 1878 25th% = 2185 50th% = 2557 75th% = 3117 90th% = 3710 95th% = 4145	POD was multiplied by an variation factor (VF) to account for variation in underlying data used to calculate DDEF (see **Appendix D**), which was defined as a custom distribution: Min = 0.31 Max = 4.3 5th% = 0.42 10th% = 0.51 25th% = 0.71 50th% = 0.99 75th% = 1.5 90th% = 2.3 95th% = 2.8 An acceptable MOE of 100, which includes consideration of a DDEF for intraspecies variation (Appendix A, Section 2) was defined based on SAP input (Appendix B)
	Chronic POD	Ovarian atrophy	Key POD was defined as the human equivalent concentration (adjusted for species differences in the internal dose of BD metabolites) corresponding to a 1% increase in extra risk of ovarian atrophy at age 60 years based on mouse and rat data combined (NTP, 1993, 1984; Owen et al., 1987; Bevan et al., 1996; Marty et al., 2021)	Custom distribution based on MSW model output that reflects uncertainty in model parameters (ppm): Min = 187 Max = 275 5th% = 195 10th% = 200 25th% = 208 50th% = 226 75th% = 248 90th% = 257 95th% = 263	POD was multiplied by a variation factor (VF) to account for variation in underlying data used to calculate DDEF (see **Appendix D**), which was defined as a custom distribution: Min = 0.69 Max = 1.6 5th% = 0.78 10th% = 0.82 25th% = 0.91 50th% = 1.0 75th% = 1.1

					90th% = 1.3 95th% = 1.4 An acceptable MOE of 150, which includes consideration of a DDEF for intraspecies variation (**Appendix A**, Section 2) was defined based on SAP input (**Appendix B**)
Cancer	Inhalation Unit Risk	Leukemia and bladder cancer (aggregate mortality) from SBR worker data (Valdez-Flores et al., 2022)	Key POD was defined as the concentration corresponding to a $1x10^{-6}$ extra cancer risk. The unit risk was calculated assuming low-dose linearity by dividing the response rate ($1x10^{-6}$) by the POD.	Custom distribution for IUR based on CPH model output that reflects uncertainty in model parameters (per ppm): Min = 7.3E-5 Max = 2.0E-4 5th% = 9.1E-5 10th% = 1.0E-4 25th% = 1.2E-4 50th% = 1.3E-4 75th% = 1.5E-4 90th% = 1.7E-4 95th% = 1.8E-4	None

Table 9. Sensitivity Analysis for Aggregate Scenarios (values reflect correlation coefficients for simulation parameters and results)

	Extra Cancer Risk			Chronic MOE			Subchronic MOE		
Risk Inputs	General Population +Worker	General Population +Smoking	General Population +Worker +Smoking	General Population +Worker	General Population +Smoking	General Population +Worker +Smoking	General Population +Worker	General Population +Smoking	General Population +Worker +Smoking
Air concentration, ambient	-0.01	0.00	-0.01	0.01	-0.03	-0.01	0.01	0.00	0.01
Air concentration, workplace	0.16		0.12	-0.20		-0.18	-0.12		-0.14
Air concentration, indoor	0.03	0.34	0.23	-0.12	-0.27	-0.31	0.01	-0.34	-0.03
Air concentration, in-vehicle	0.02	0.10	0.07	-0.03	-0.08	-0.09	0.00	-0.10	0.00
Breathing rate ratio, noncancer				-0.15		-0.14	-0.09	-0.23	-0.13
Exposure time	-0.03	-0.07	-0.06	0.02	0.04	0.06	0.02	0.05	0.02
Exposure time, in-vehicle	0.00	0.00	0.00	0.00	-0.01	0.00	0.01	0.01	0.01
Exposure time, work	0.10	-0.03	0.05	-0.10	0.02	-0.07	-0.08	0.02	-0.08
Exposure frequency	0.01	0.05	0.04	-0.01	-0.03	-0.03	0.01	-0.04	0.01
Exposure frequency, in-vehicle	0.01	0.04	0.03	-0.03	-0.05	-0.05	-0.02	-0.06	-0.03
Exposure frequency, work	0.09	-0.02	0.06	-0.09	0.02	-0.05	-0.06	0.03	-0.06
Exposure duration, chronic	0.11	0.85	0.60	0.28	-0.38	-0.05	-0.02	-0.06	-0.02
Exposure duration, subchronic							0.09	0.00	0.10
Exposure duration, work	0.39	-0.08	0.23	-0.32	0.30	-0.01	-0.30	0.06	-0.33
Biomarker, smokers		0.02	0.01		-0.02	-0.02		-0.02	0.00
Biomarker, nonsmokers		-0.01	-0.01		0.01	0.02		0.01	-0.01

Respirator protection factor	-0.35		-0.25	0.61		0.45	0.46		0.46
POD, chronic noncancer				0.14	0.08	0.18			
POD, subchronic noncancer							0.14	0.30	0.19
Interspecies adjustment, chronic				0.22	0.15	0.31			
Interspecies adjustment, subchronic							0.34	0.71	0.44
Inhalation unit risk	0.15	0.23	0.25						

Highlighted cells indicate parameters with correlation coefficients greater than 0.1 (green) or less than -0.1 (orange)

Figure 1. BD Urinary Biomarker (4HEBMA) in Smokers and Nonsmokers (NHANES 2011-18); The arithmetic mean (indicated by column height) for for 4HEBMA in smokers is approximately 6.4 higher than the arithmetic mean in nonsmokers

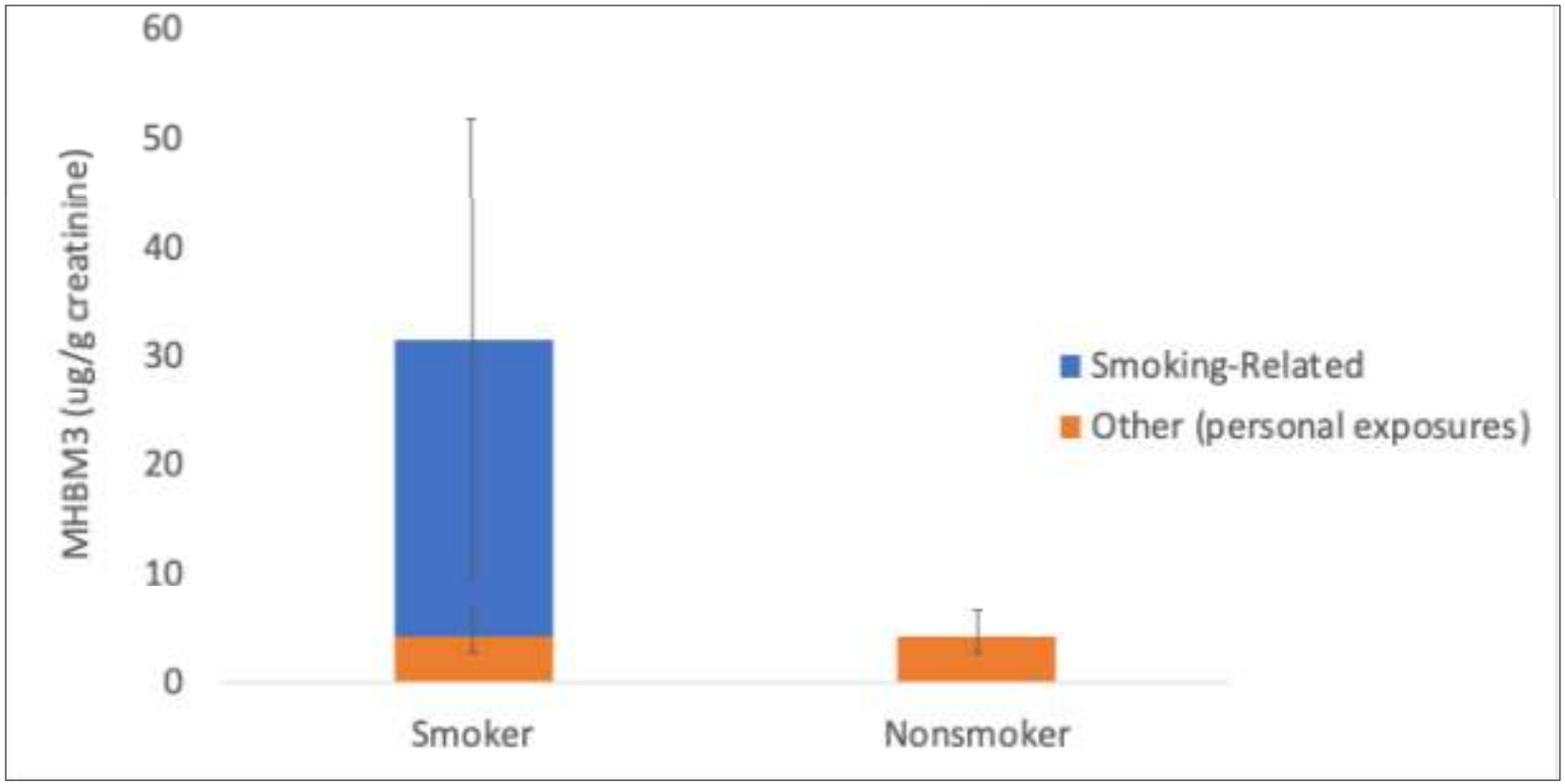


Figure 2. BD Releases Based on USEPA National Emissions Inventory (USEPA, 2020c): Total Sources = 1.0E+08 lbs

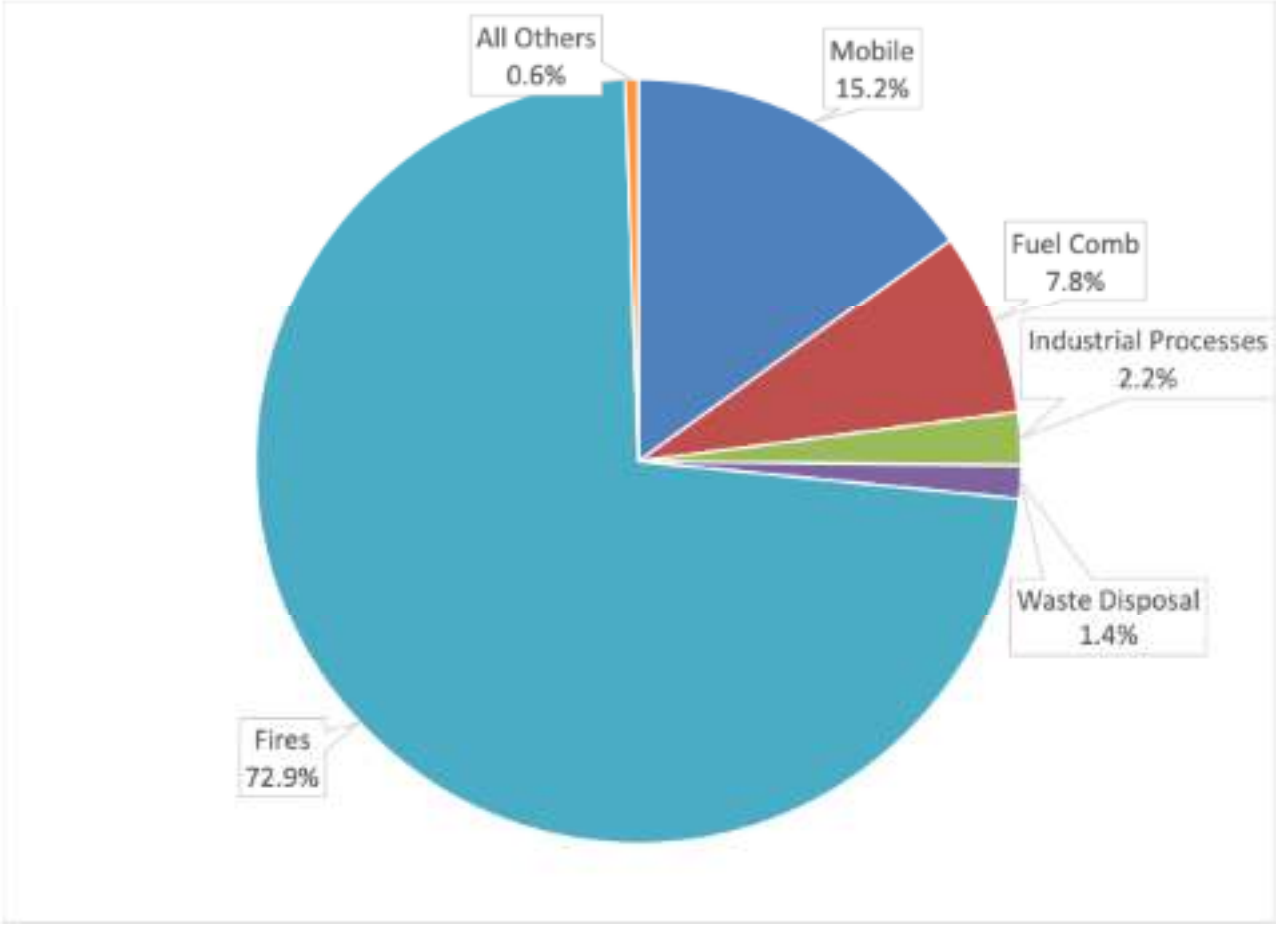
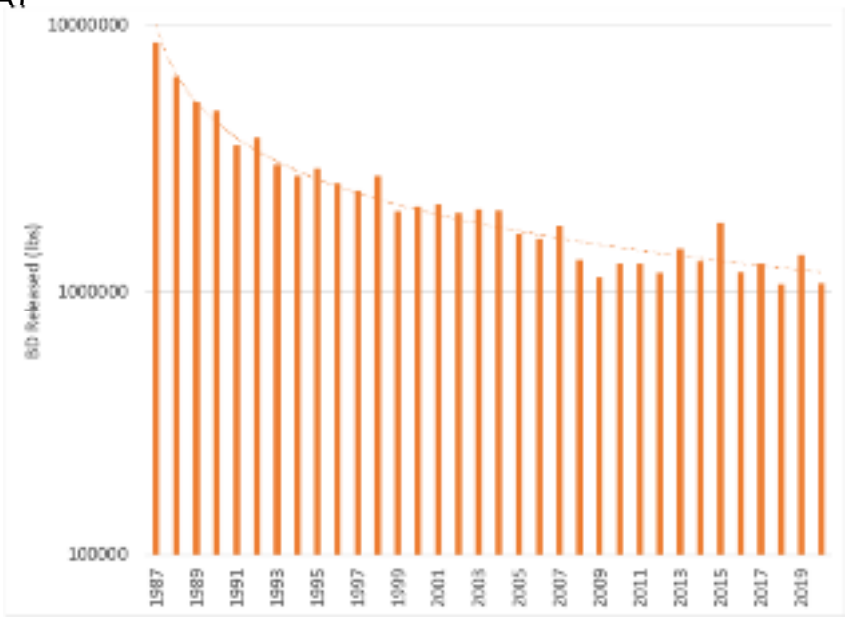


Figure 3. Historical Trends for (A) Industry BD Emissions (USEPA, 2020c) and (B) Concentrations in Ambient Air (USEPA, 2020d)

(A)



(B)

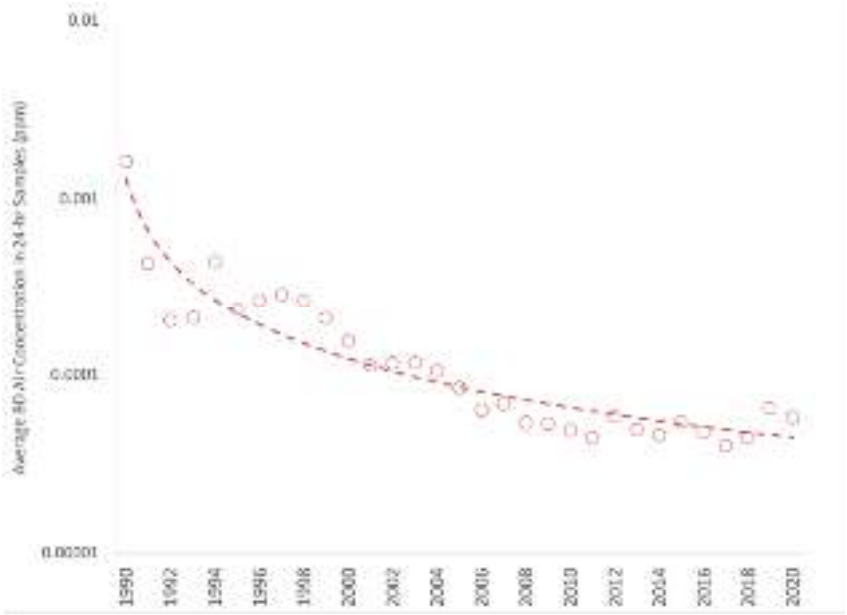
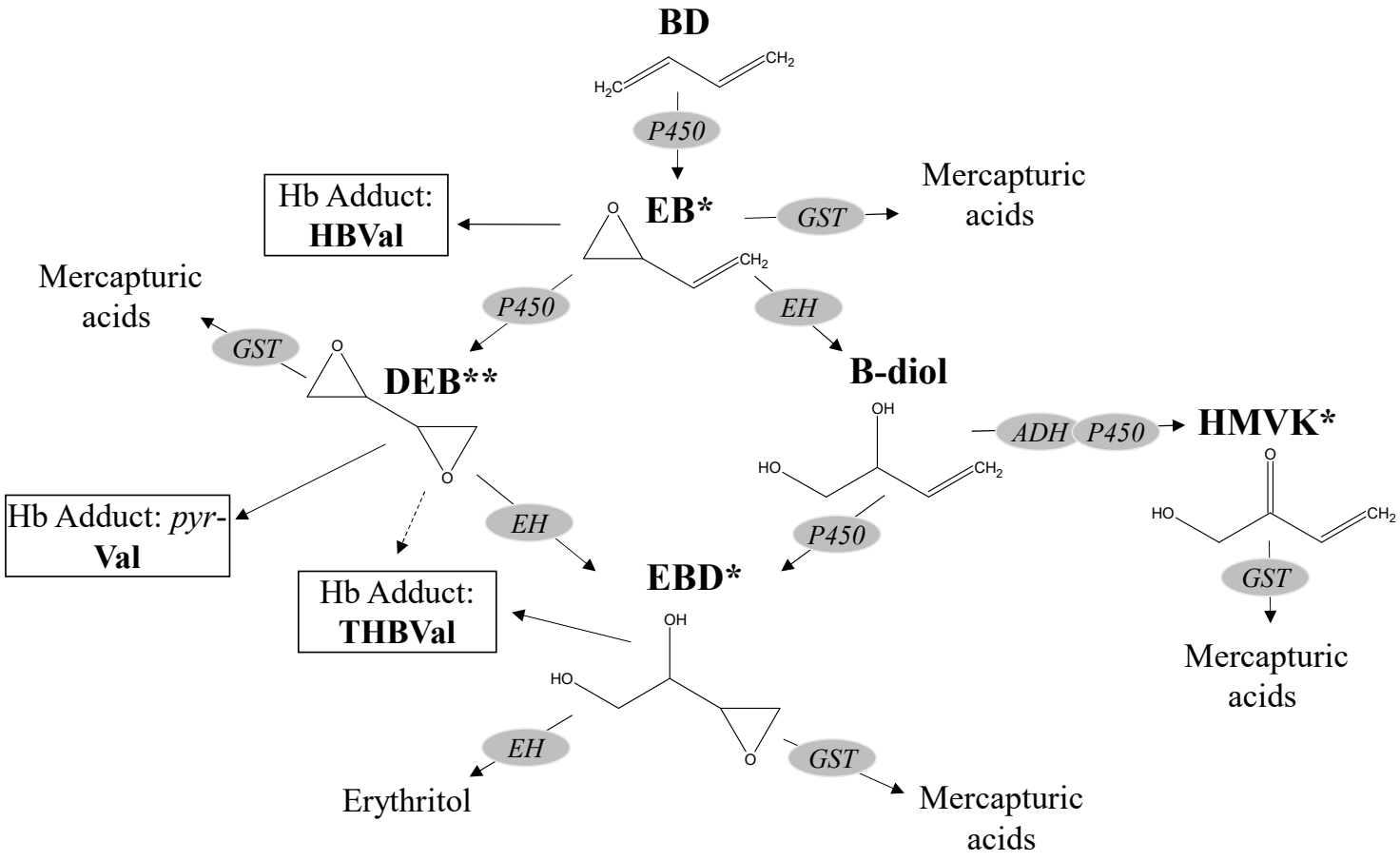


Figure 4. Metabolism of BD to Reactive Epoxides



*monofunctional alkylating agent; **bifunctional alkylating agent

Figure 5. Detailed Results for Worker 1 Exposure Scenario

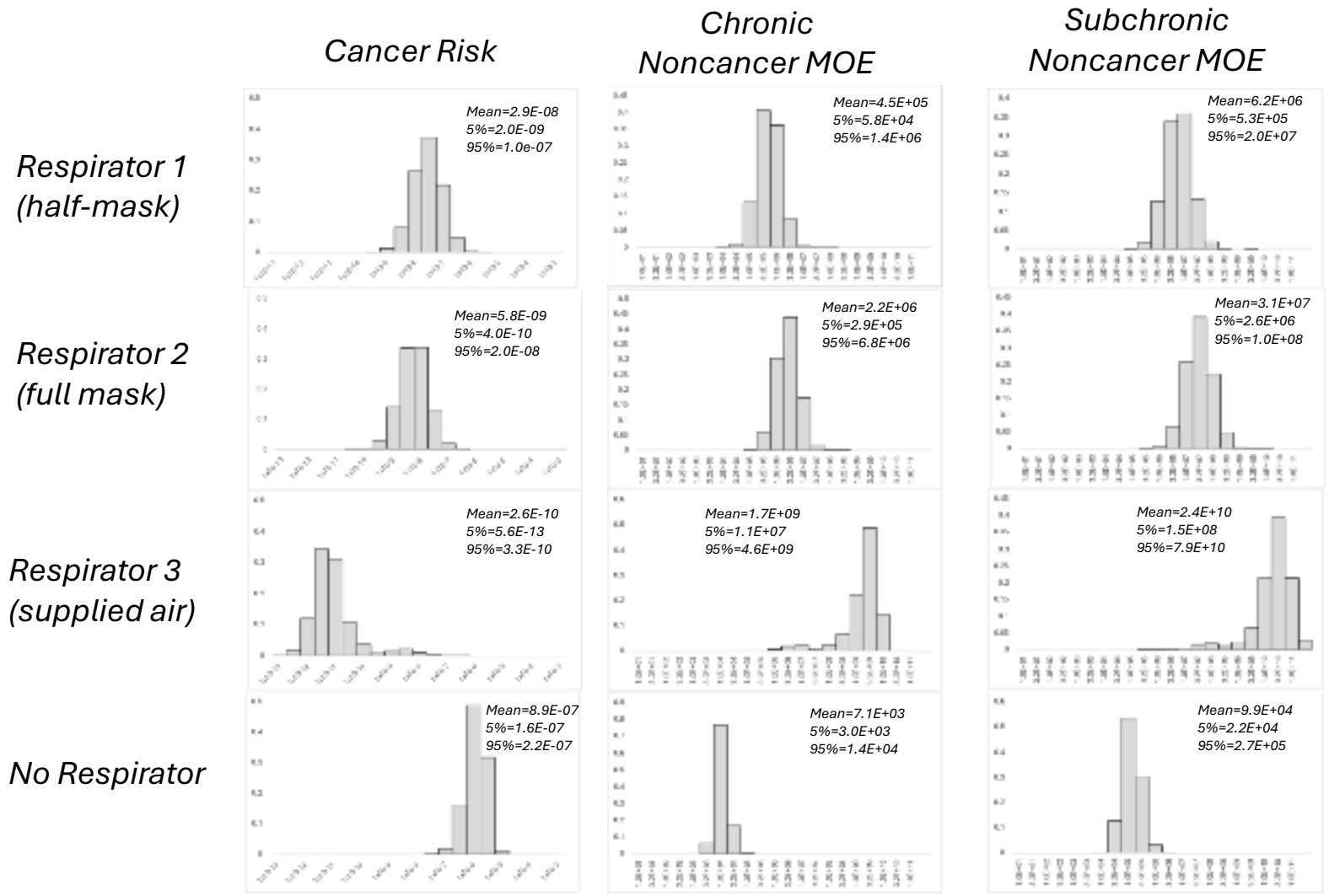


Figure 6. Summary of Risk Results for Worker Exposure Scenarios. X = arithmetic mean; error bars = 5th - 95th percentiles; solid blue line = 1x10^{-4} risk level; shaded region = 1x10^{-6} to 1x10^{-4} risk range

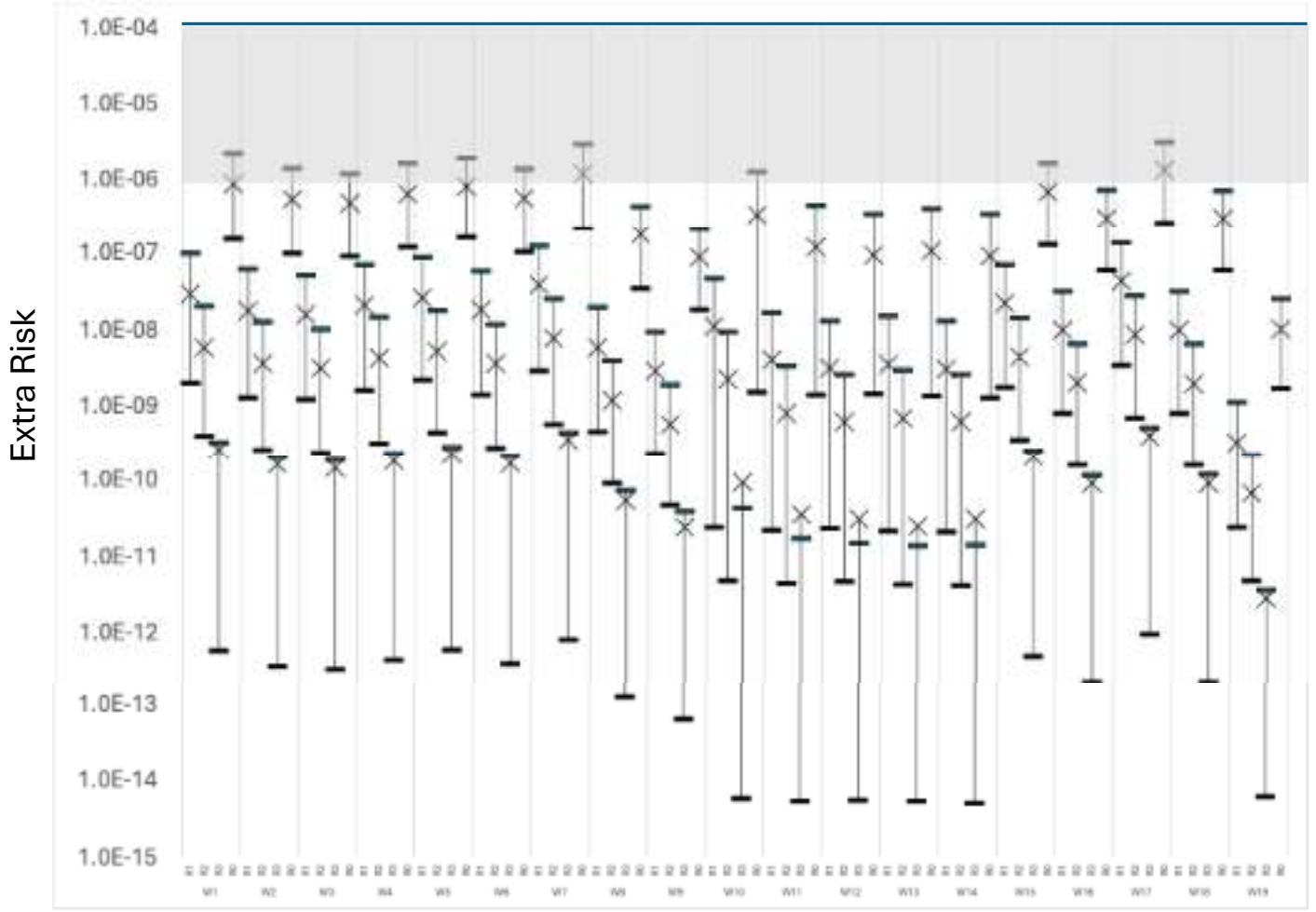


Figure 7. Summary of Risk Results for Aggregate Exposure Scenarios. X = arithmetic mean; error bars = 5th - 95th percentiles; solid blue line = 1x10^{-4} risk level; shaded region = 1x10^{-6} to 1x10^{-6} risk range

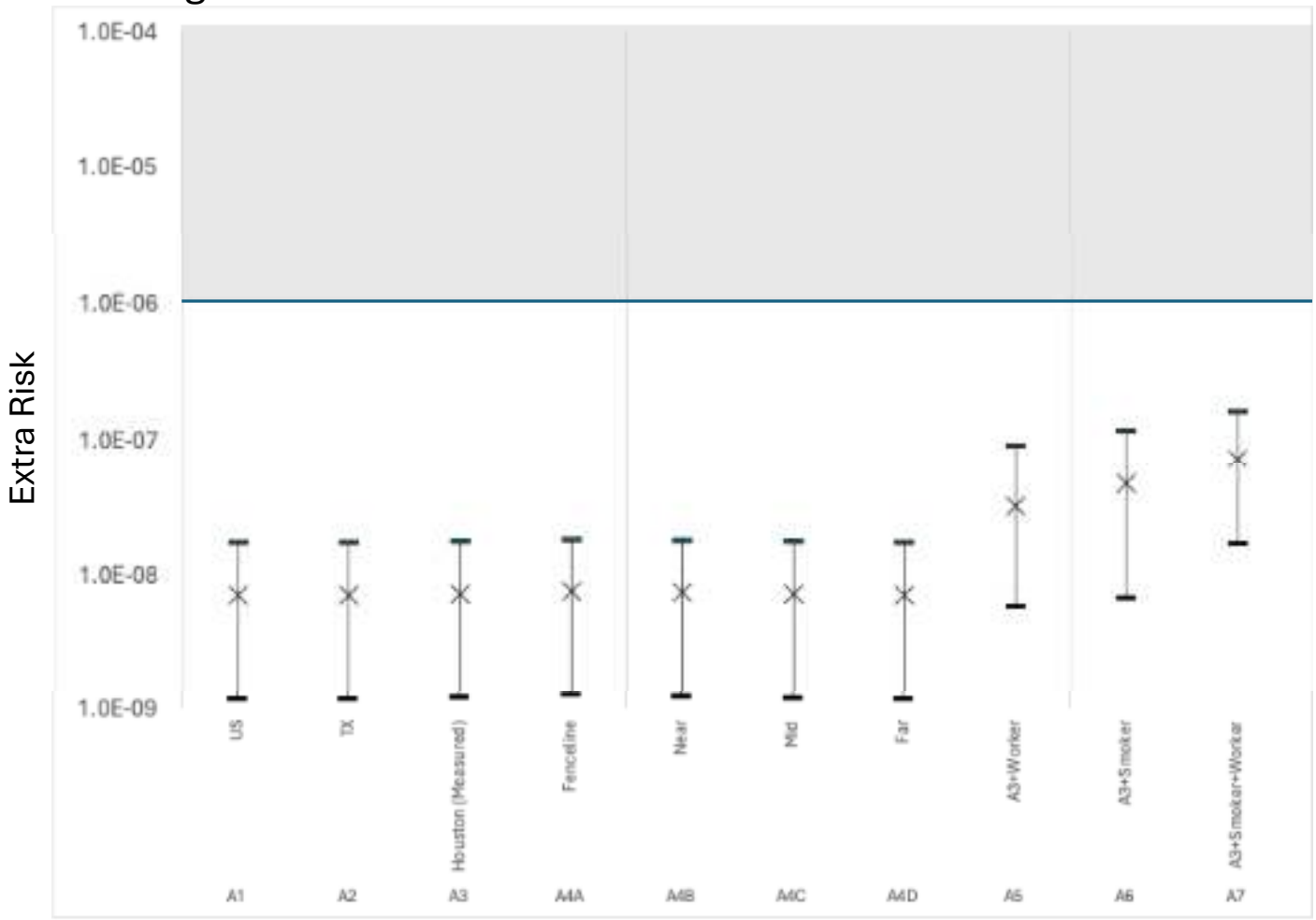


Figure 8. Summary of Chronic MOE Results for Worker Exposure Scenarios. X = arithmetic mean; error bars = 5th - 95th percentiles; solid blue line = acceptable MOE of 150

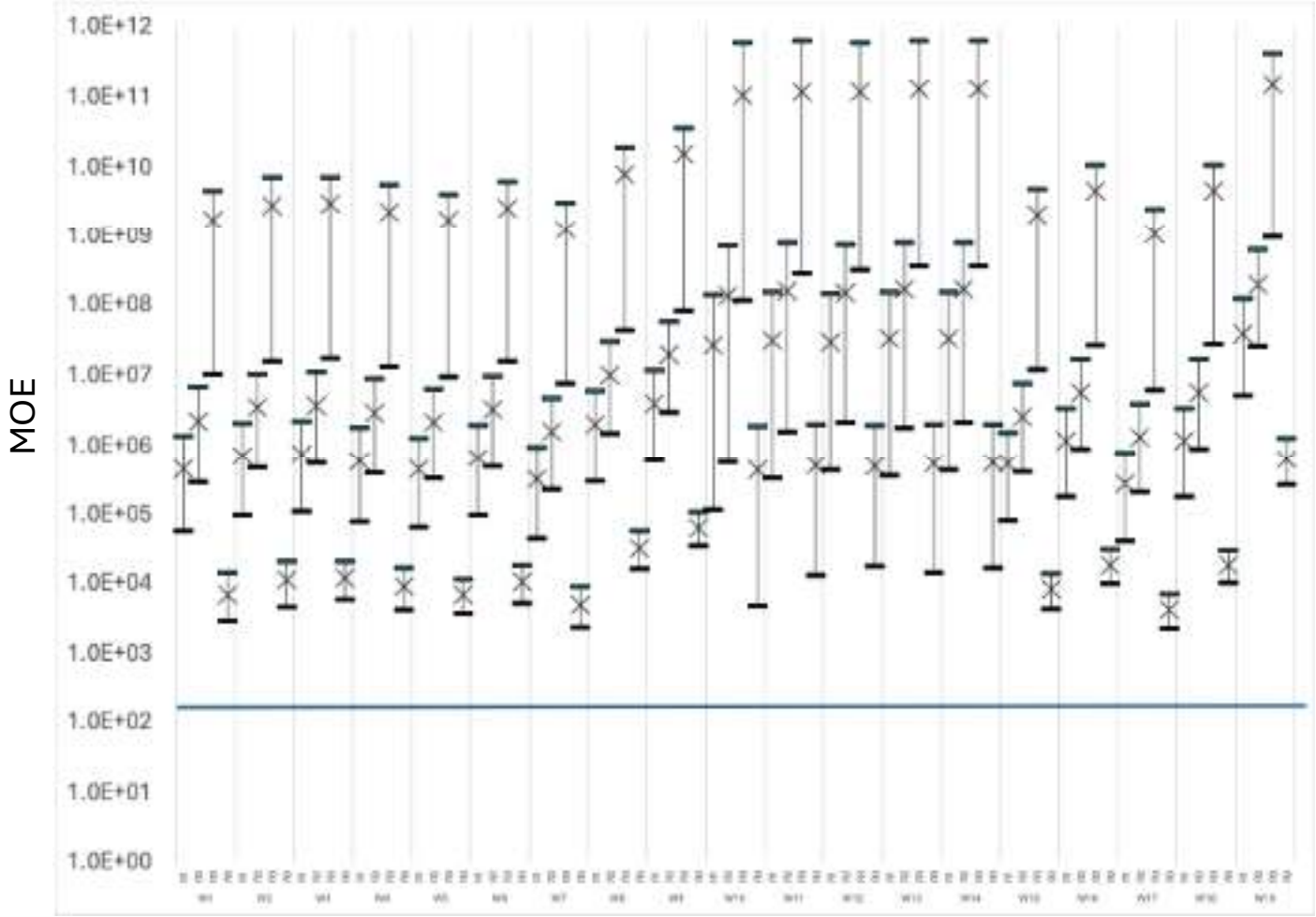


Figure 9. Summary of Chronic MOE Results for Aggregate Exposure Scenarios. X = arithmetic mean; error bars = 5th - 95th percentiles; solid blue line = acceptable MOE of 150

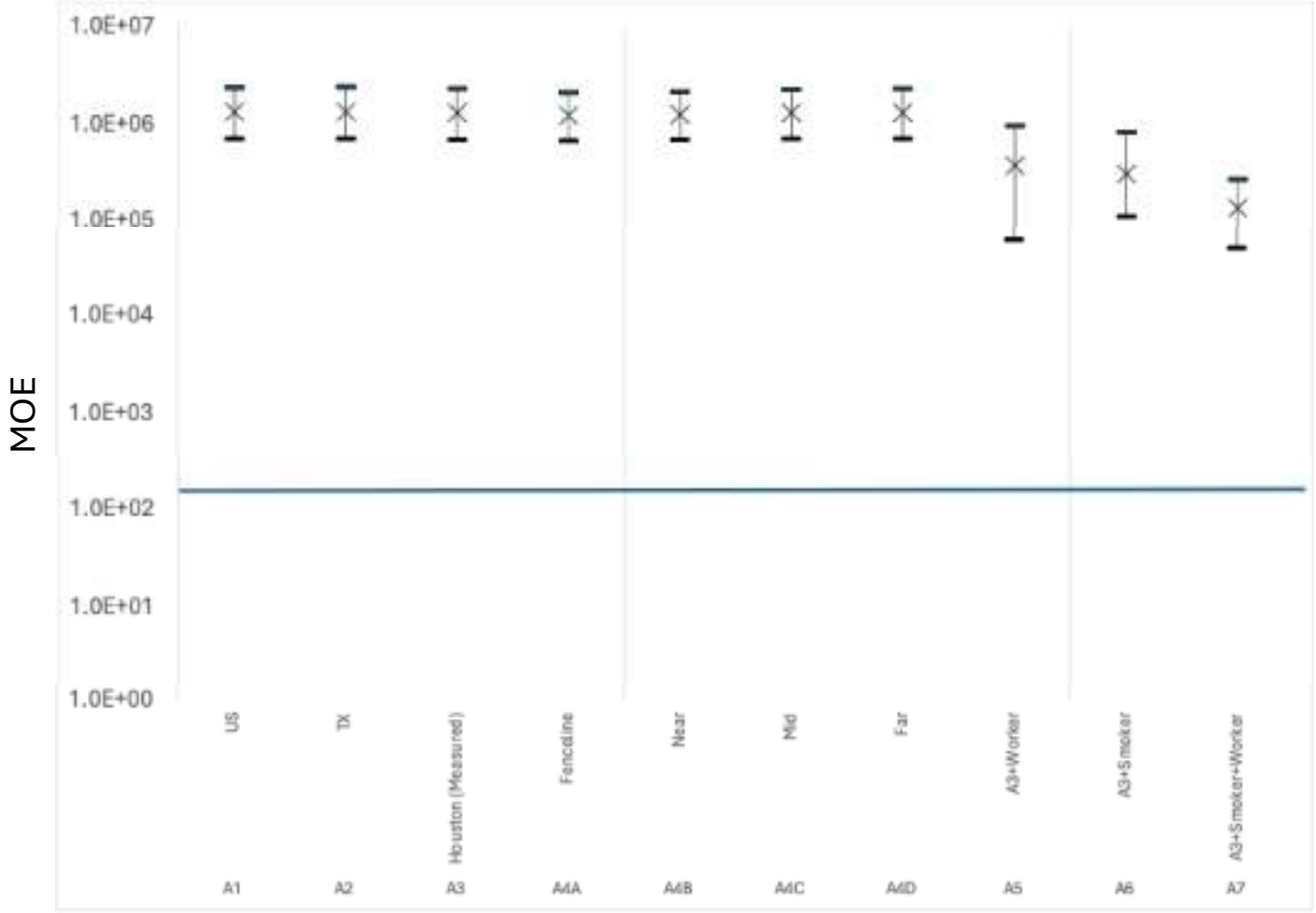


Figure 10. Summary of Subchronic MOE Results for Worker Exposure Scenarios. X = arithmetic mean; error bars = 5th - 95th percentiles; solid blue line = acceptable MOE of 100

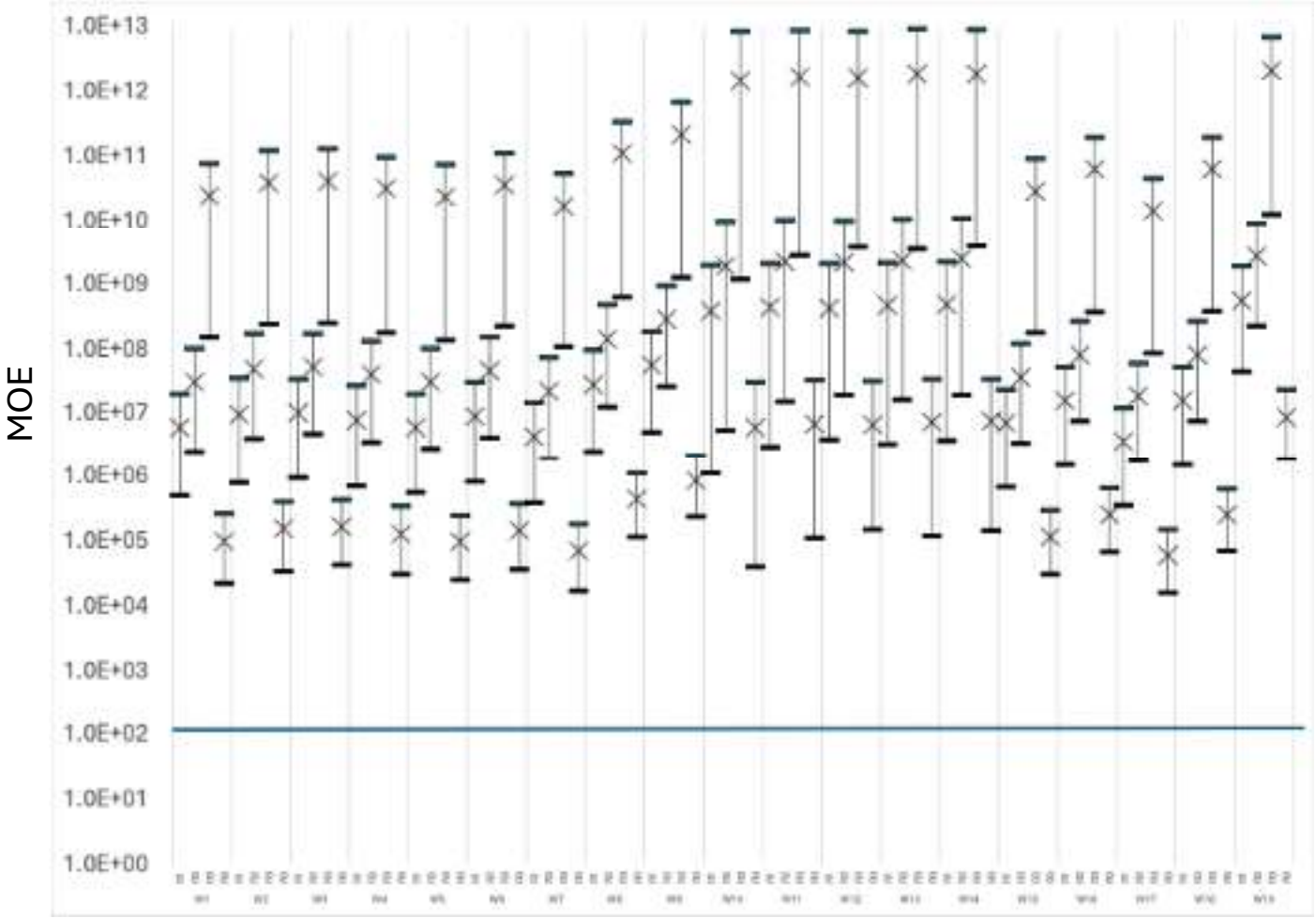


Figure 11. Summary of Subchronic MOE Results for Aggregate Exposure Scenarios. X = arithmetic mean; error bars = 5th - 95th percentiles; solid blue line = acceptable MOE of 100

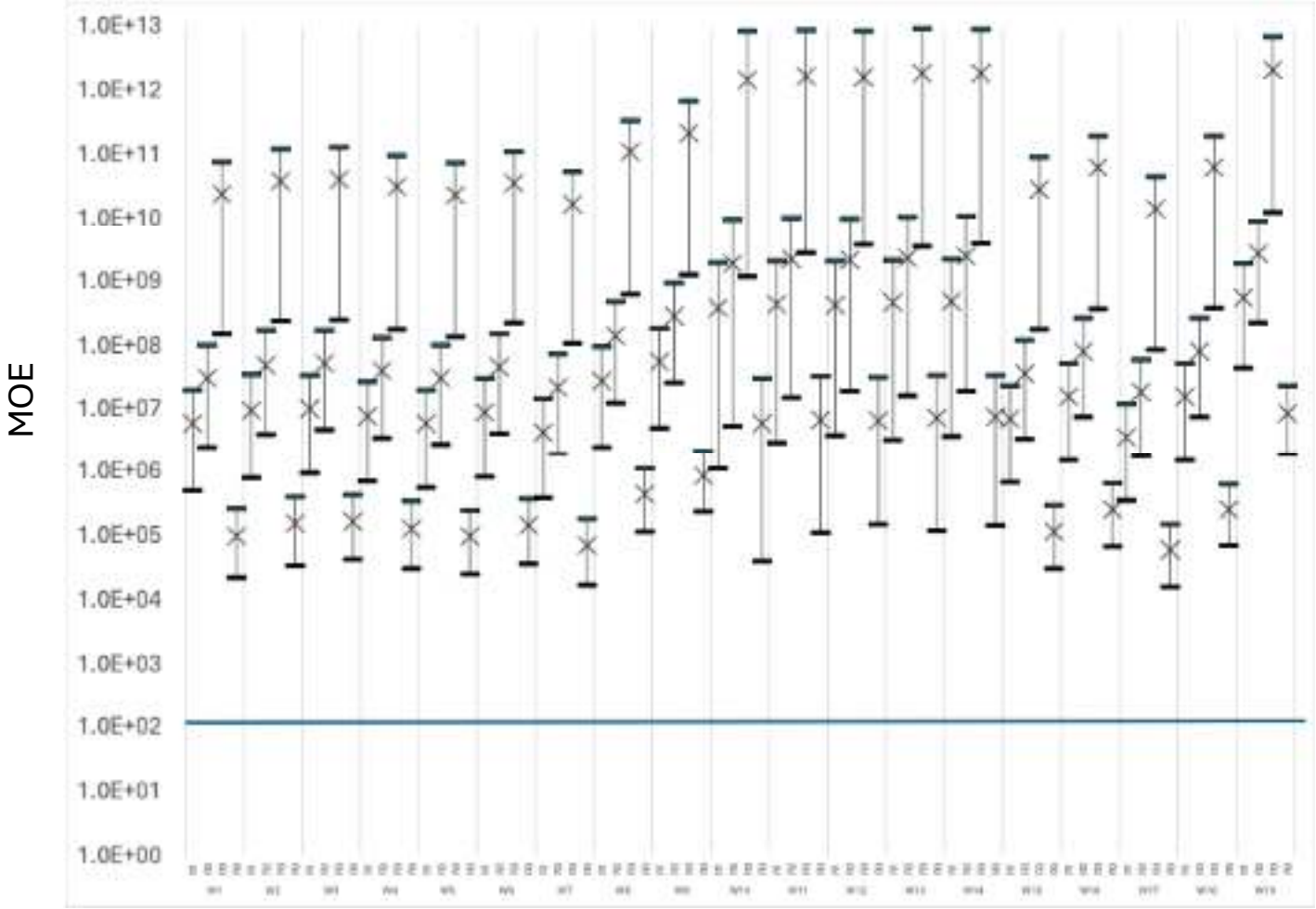
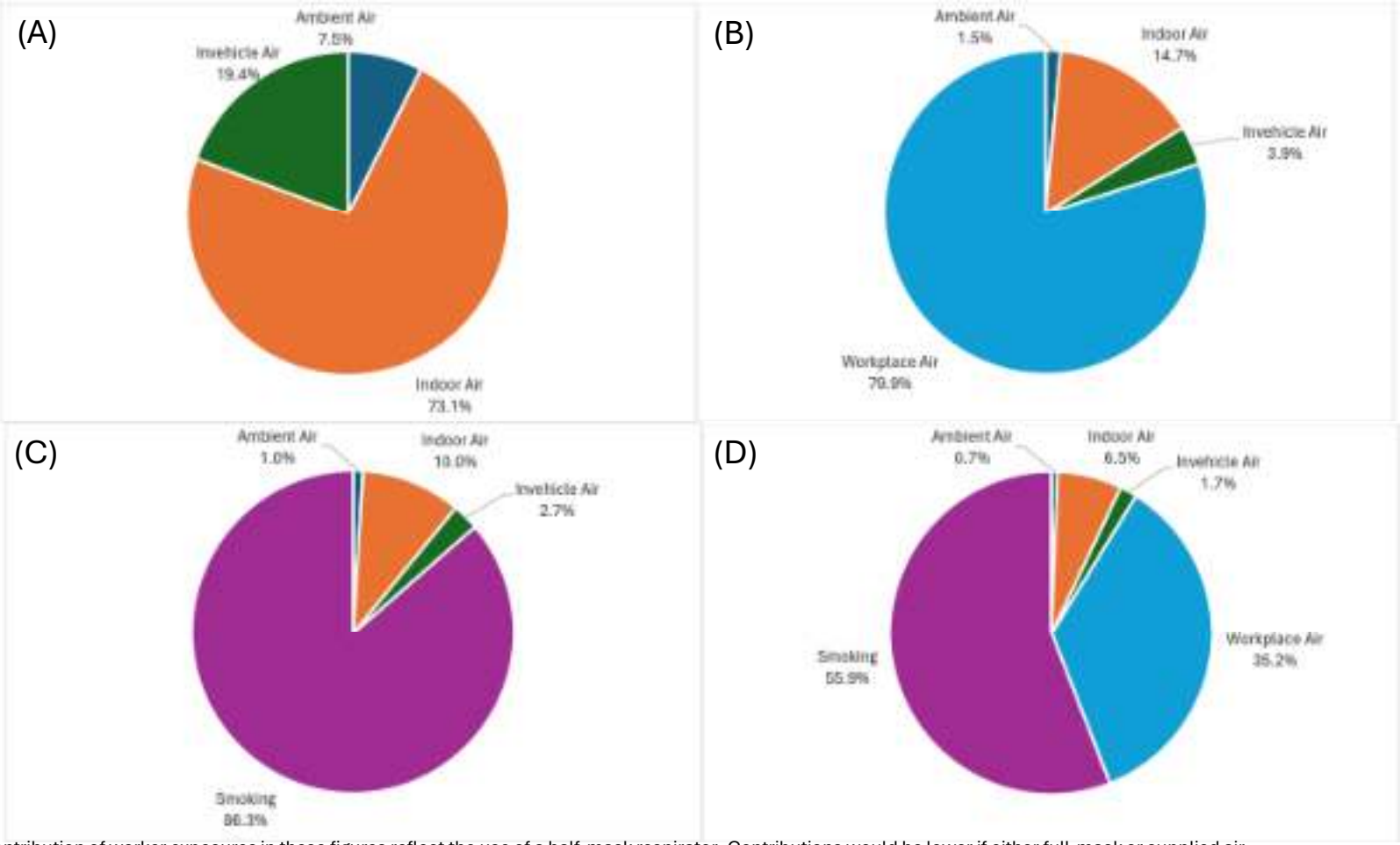


Figure 12. Pathway Contribution to Aggregate Exposure Scenarios: (A) A3 = General Population Exposures; (B) A5 = General Population + Worker* Exposures; (C) A6 = General Population + Smoking Exposures ; (D) A7 = General Population + Worker* + Smoking Exposures



*The contribution of worker exposures in these figures reflect the use of a half-mask respirator. Contributions would be lower if either full-mask or supplied air respirators were assumed, and would be higher if no respirator was assumed.

Figure 13. Comparison of Occupational Exposure Value Frequency Distributions to Existing OSHA PEL for 1,3-Butadiene

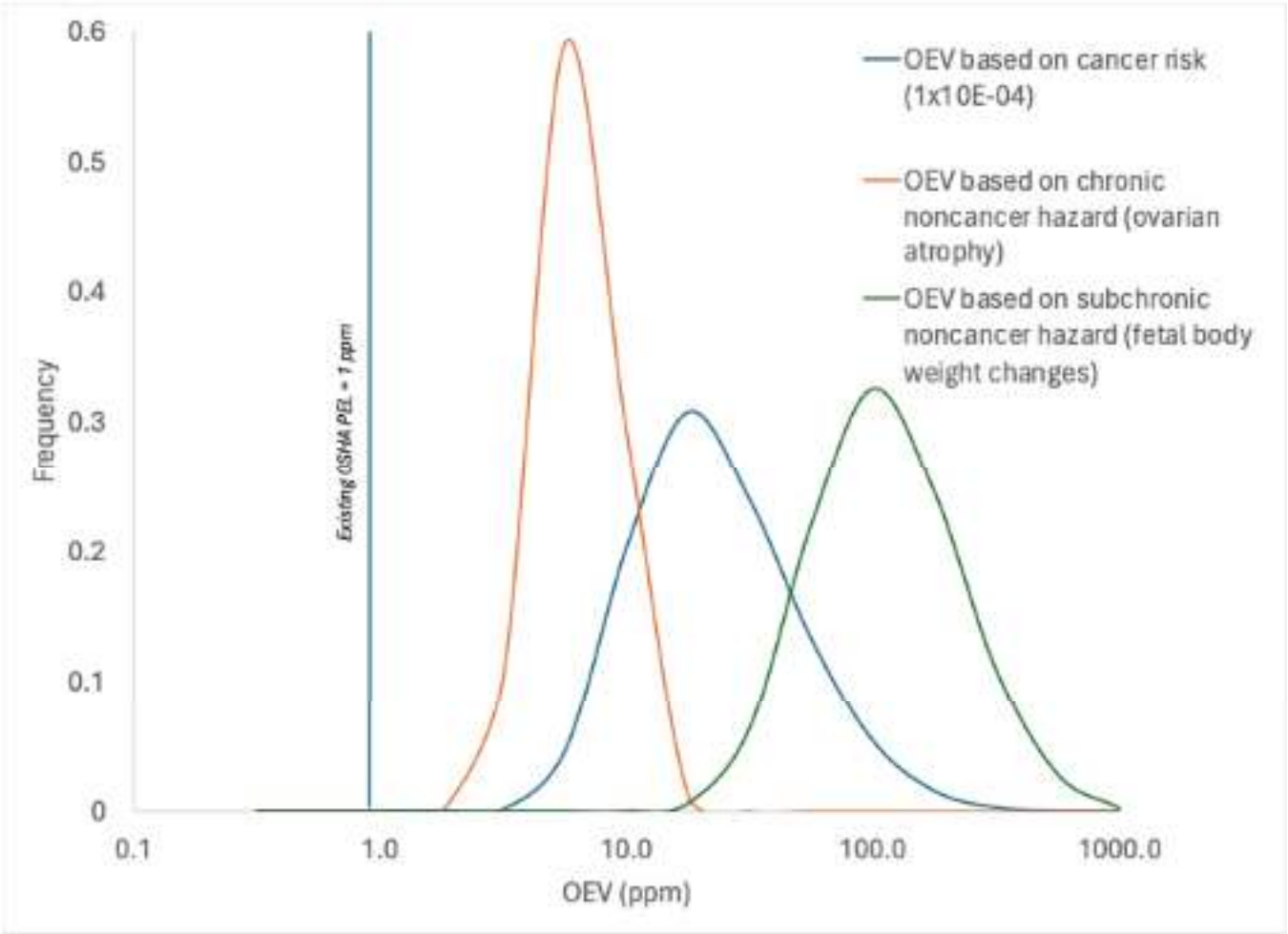


Figure 14. Acute Noncancer Screening Analysis for Worker Scenarios. Columns indicate the maximum reported concentration, as affected by respirator use; red line = AEGL-1 value of 670 ppm (USEPA, 2009); yellow line = subchronic RfC of 57 ppm (Kirman et al., 2022)

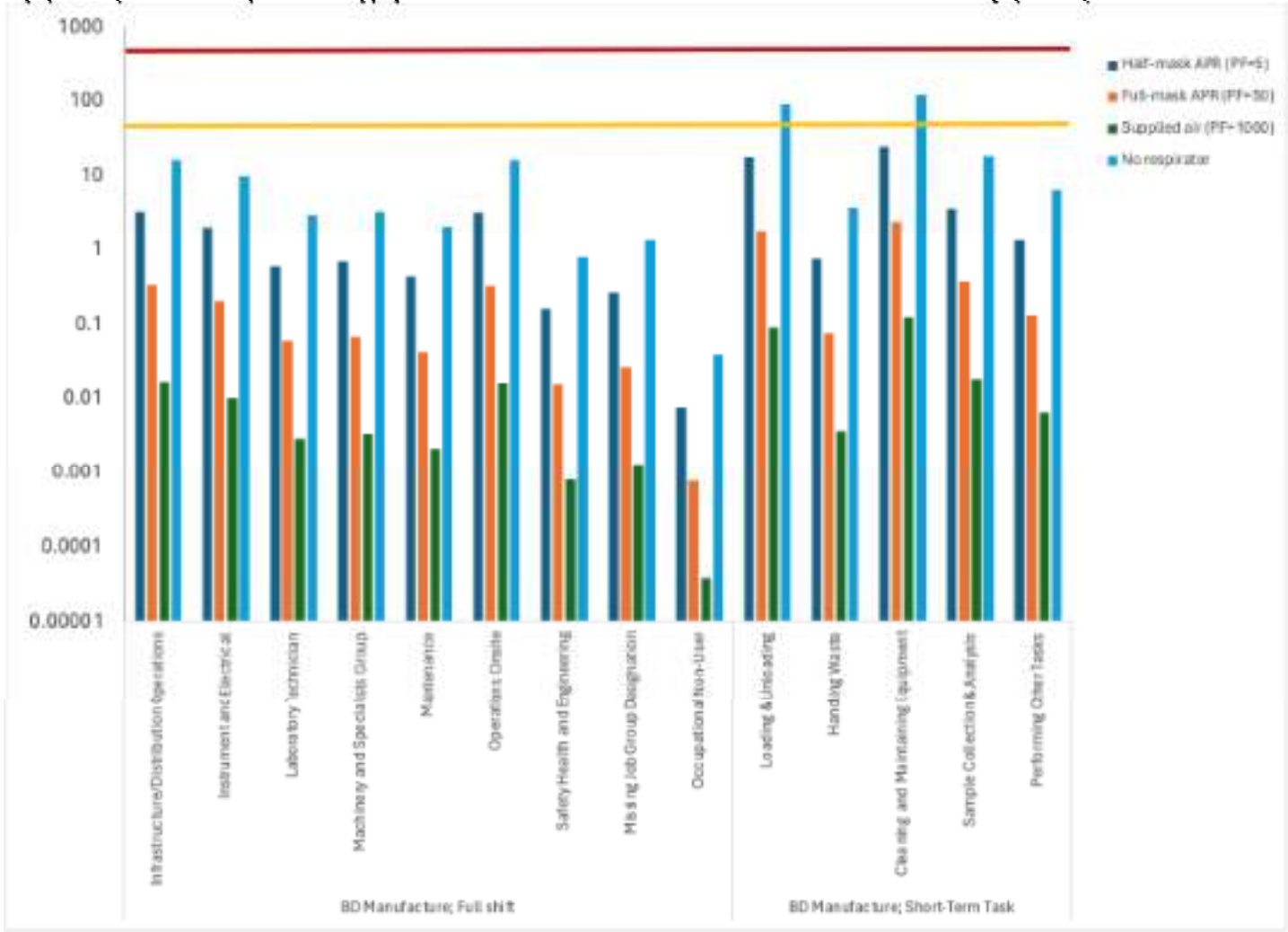
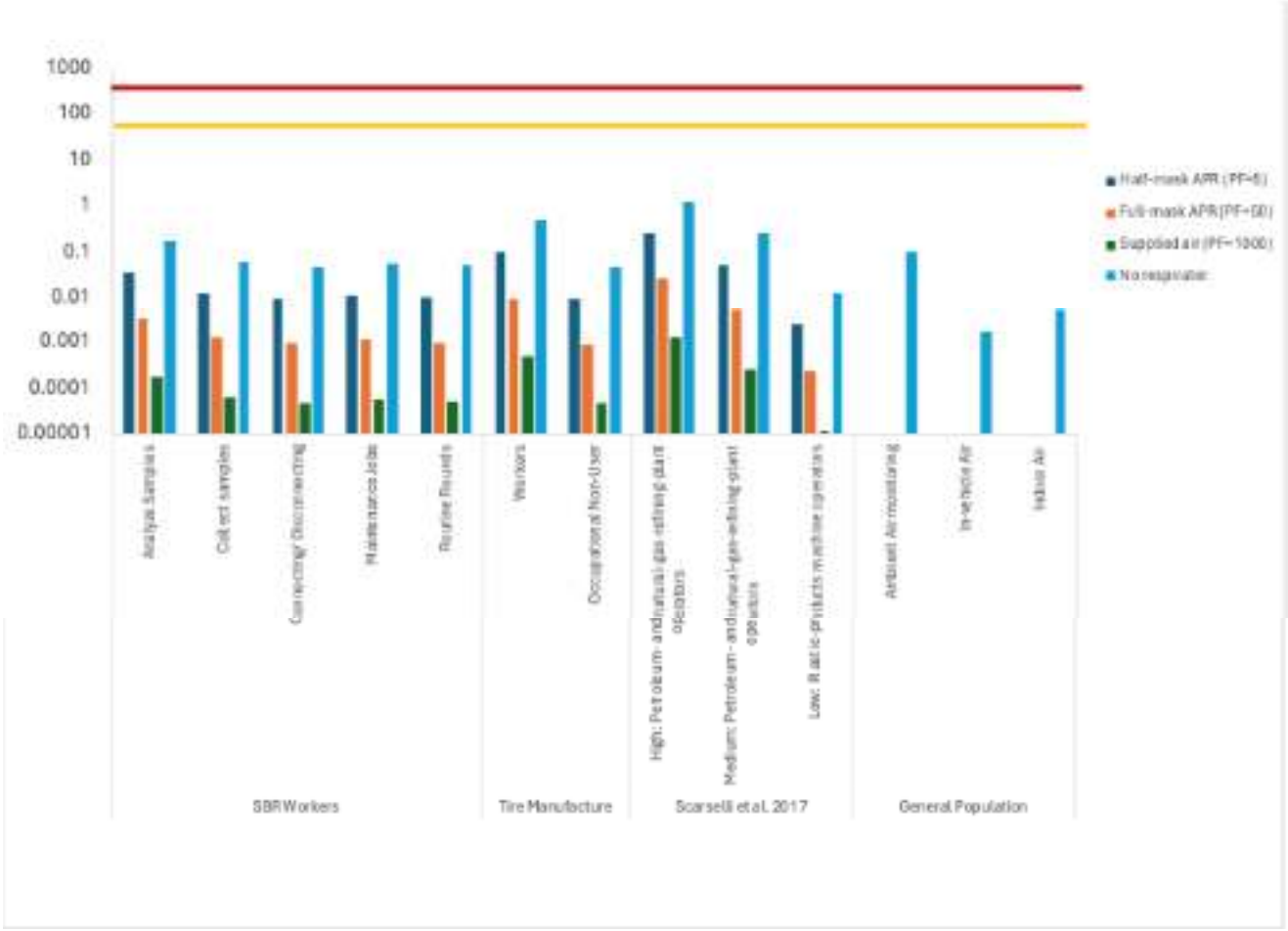


Figure 15. Acute Noncancer Screening Analysis for Other Worker and General Population/Aggregate Scenarios. Columns indicate the maximum reported concentration, as affected by respirator use; red line = AEGL-1 value of 670 ppm (USEPA, 2009); yellow line = subchronic RfC of 57 ppm (Kirman et al., 2022)



Appendix A: Review Material for the Science Advisory Panel for 1,3-Butadiene Risk Assessment

The text below represents summary material that was provided to the independent Science Advisory Panel (SAP) for their review along with access to underlying publications and reports. The SAP panel review consistent of 5 rounds of engagement (Rounds 1, 3, and 5 consisted of reviewing material and answering charge questions; Rounds 2 and 4 consisted of commenting and debate on the charge question responses, and did not include additional review material). The text is organized into the following sections:

- Section 1: Review Material for Round 1
- Section 2: Review Material for Round 3
- Section 3: Review Material for Round 5

The review material was provided to the SAP as three separate documents that were merged together in this appendix. Minor changes were made to the text below to renumber tables and figure to avoid confusion from duplicate numbering.

1. Summary Material for Round 1

The text below is intended to provide a high-level summary of data and issues related to exposures to 1,3-butadiene (BD) in the United States, including its chemical-physical properties, exposure, and toxicity values.

1.1. Chemical-Physical Properties

- BD (CAS No. 106-99-0) is a colorless gas with a mild aromatic or gasoline odor at ambient temperature and pressure. Its molecular formula is C4H6. BD is a building block chemical that is reacted or polymerized and may be further processed to create a range of materials that can be used to make downstream consumer goods.
- Based on physical chemical (PC) properties (high Henry's law, vapor pressure, low-to-insoluble in water, (**Table 1-1**; adapted from USEPA's *Final Scope of the Risk Evaluation for 1,3-Butadiene*) 1,3-butadiene (BD) is a highly volatile gas at standard temperature and pressure.
- Due to these properties, inhalation of BD in air is expected to be the primary (and near exclusive) route of exposure.
- Due to these properties BD poses several potential physical hazards.
    - At high air concentrations it is highly flammable and susceptible to ignition due to its extremely low flash point. Its vapors are heavier than air and a flame can flash back to the source of leak very easily.
    - Contact with the liquid BD, which requires low temperatures and/or high pressure, can cause frostbite.

- At high concentrations BD can cause asphyxiation by displacement of oxygen in air.

- A separate white paper has been prepared that covers the chemical-physical properties, manufacture, and use of BD (unpublished white paper: *1,3-Butadiene Overview*).

Table 1-1: Select Physical-Chemical Properties of BD

Property or Endpoint	Value[a]	Reference	Data Quality Rating
Molecular formula	C4H6	NA	NA
Molecular weight	54.09 g/mol	NA	NA
Physical state	Colorless gas	Rumble (2018a)	High
Physical properties	Colorless, mildly aromatic or gasoline- like odor	NLM (2003)	High
Melting point	-108.966°C	O'Neil (2013)	High
Boiling point	-4.5°C at 760 mm Hg	O'Neil (2013)	High
Density	0.6149 g/cm3 at 25°C and >1 atm	Rumble (2018a)	High
Vapor pressure	2110 mm Hg	U.S EPA (2019b)	High
Vapor density	1.87 (air = 1)	NLM (2003)	High
Water solubility	735 mg/L at 20°C	NLM (2003)	High
Octanol/water partition coefficient (log Kow)	1.99 at 25°C	Rumble (2018c)	High
Henry's Law constant	0.204 atm·m3 /mol at 25°C	Rumble (2018b)	High
Flash point	-76.111°C	RSC (2019)	High
Auto flammability	420°C	Rumble (2018a)	High
Viscosity	0.00754 cP at 20°C	NLM (2003)	High
Refractive Index	1.4292	Rumble (2018a)	High
Dielectric constant	2.050	Rumble (2018a)	High

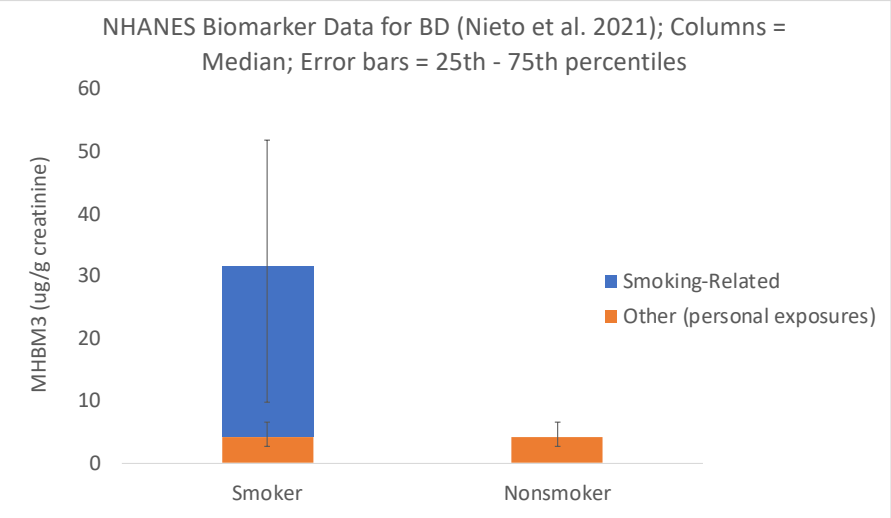
[a] Measured unless otherwise noted.
NA = Not applicable

1.2. BD Exposure Summary

1.2.1 BD Exposure is Ubiquitous and Smoking is the Largest Non-Occupational Source of Exposure in the United States

- Essentially all people are exposed to BD in some manner based on urinary biomarker detection rates greater than 96% of samples collected as part of the Nation Health and Nutrition Examination Survey (NHANES) in United States (Nieto et al. 2021). These biomarker measurements reflect total exposure to BD (i.e., across all exposure pathways for recent exposures to BD).
- Smoking represents the single largest non-occupational source of BD exposure to the US population. Urinary biomarkers (N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine or MHBMA3) measured in smokers are on average approximately 7.5-fold higher (31.5 vs 4.11 ug/g creatinine) than corresponding levels measured in nonsmokers (**Figure 1-1**).
- Biomarker measurements in nonsmokers reflect recent personal exposures to BD (e.g., ambient air, indoor air, in-vehicle air, etc.).

Figure 1-1. BD Urinary Biomarkers in Nonsmokers and Smokers (NHANES 2011-16; Nieto et al. 2021)



- Smoking exposures to BD in the US have decreased over time due to trends in smoking behaviors (**Table 1-2**), such that exposures to BD from smoking were considerably larger in the past than were measured in NHANES 2011-2016. This decreasing trend is expected to continue in the future. The estimated mean (based on changes in smoking habit, and a correlation between biomarker concentration in urine and cigarettes per day (CPD)) in this table for smokers in 2015 (25 ug/g creatinine) matches well with measured values reported for smokers in NHANES 2011-16 (median = 31.5 ug/g creatinine; Nieto et al. 2021)

Table 1-2. Estimated BD Biomarker Based on Trends in Smoking Behavior in the US

	Smoking Intensity (% of smokers that fall into each cigarette-per-day (CPD) category)*				Urinary MHBMA3 (ug/g creatinine)		
Year	**High (>24 CPD)**	**Medium (15-24 CPD)**	**Low (<15 CPD)**	**Smoking Prevalence (%)***	**Smoker Estimated Mean****	**Nonsmoker Estimated Mean*****	**Estimated US Population Mean (smokers and nonsmokers combined)**
1975	25.9	43	31.2	37.1	35	4.1	15.5
1980	29.1	42.1	28.2	33.2	36	4.1	14.7
1985	26.6	41.8	31.6	30.1	35	4.1	13.4
1990	22.9	42.6	34.5	25.5	34	4.1	11.7
1995	20.1	39	40.9	24.7	32	4.1	11.0
2000	15.4	38.8	45.8	23.3	30	4.1	10.2
2005	11.7	36.6	51.7	20.9	28	4.1	9.2
2010	7.4	33.7	58.9	19.3	26	4.1	8.4
2015	6.4	29.7	63.9	15.1	25	4.1	7.3

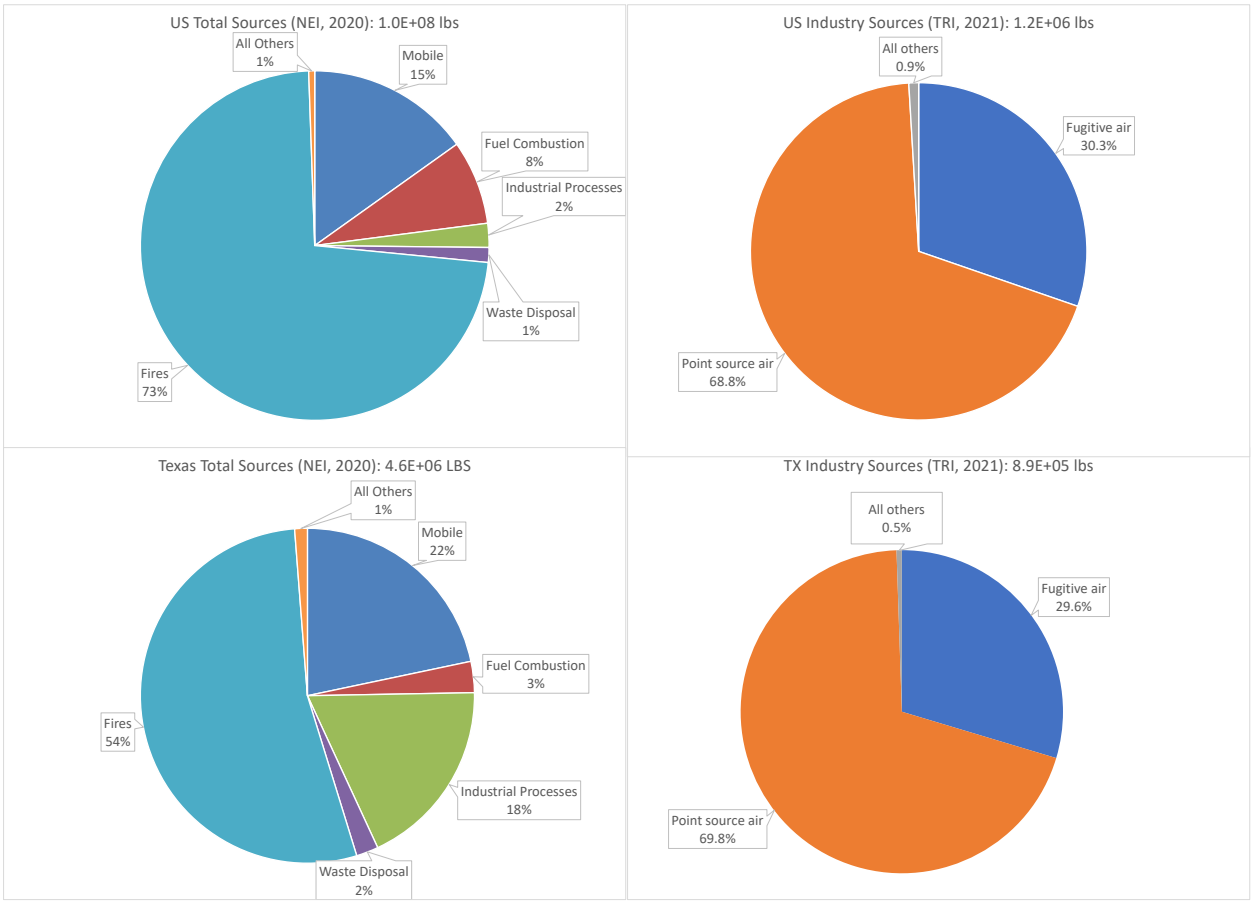
*American Lung Association (ALA, 2020)

**Estimated from smoking intensity data and a correlation between urinary MHBMA3 and CPD based on data reported in Nieto et al. (2021).
***Assumed constant over time

1.2.2 Based on Release Data Inhalation is the Primary Route by Which the US Population is Exposed to BD

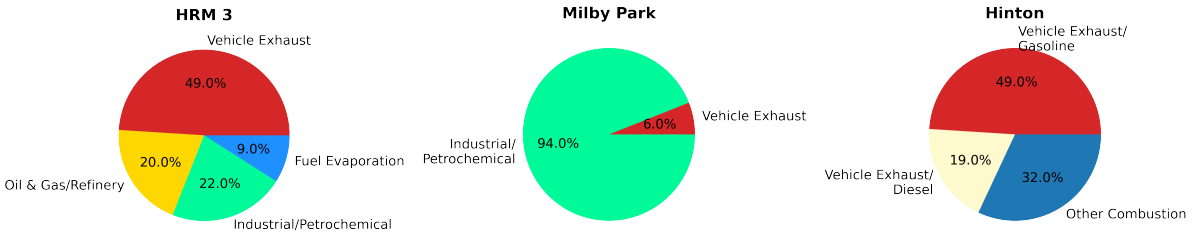
- In addition to the physical-chemical properties of BD (**Table 1-1**) which favor the inhalation pathway, release information indicate that air is the predominant exposure media since >99% of known BD releases are directly to air.
    - US Data:
        - EPA National Emissions Inventory database (EPA NEI, 2020) reports that over 1E+08 lbs of BD were released, of which fires (73%) and mobile sources (e.g., fuel combustion from cars and trucks) (15%) represent the largest sources, and releases associated with industrial processes and disposal (3.6% combined) represent a small source in the US (**Figure 1-2**).
        - EPA Toxics Release Inventory database (EPA TRI, 2021) reports that over 1.2E+06 lbs of BD were released as a result of industrial processes, of which point source releases (69%) and fugitive air releases (30%) were the largest sources, with all others were negligible (<1%) (**Figure 1-2**).
        - It should be noted that industrial emission estimates from these two data sources are similar but not an exact match, due to differences in reporting requirements and practices.
    - Texas Data:
        - In Texas, as a state that produces a large portion of BD in the US, NEI (2020) reports that over 4.6E+06 lbs of BD were released, of which fires (54%), mobile sources (22%), and industrial processes and disposal (21% combined) represent the largest sources (**Figure 1-2**).
        - EPA Toxics Release Inventory database (TRI, 2021) reports that over 8.8E+05 lbs of BD were released in Texas as a result of industrial processes, of which point source releases (70%) and fugitive air releases (30%) were the largest sources, with all others being negligible (<1%) (**Figure 1-2**).
        - As noted above for national estimates, industrial emission estimates at the state level from these two data sources are similar but not an exact match, due to differences in reporting requirements and practices.

Figure 1-2. BD Releases Based on (A) EPA National Emissions Inventory (NEI, 2020) and (B) Toxics Release Inventory (TRI, 2021)



- Based on its physical-chemical properties (e.g., boiling point of -4.5 C; **Table 1-1**), the relatively small amounts of BD released to media other than air (e.g., water, soil) are expected to rapidly volatilize to air.
- At the local level, the relative importance of different emissions sources to air concentrations is highly site-specific, depending on proximity to industrial and other sources (e.g., highways) of BD, as indicated by air modeling results for three locations in the Houston, TX area (**Figure 1-3**).

Figure 1-3. Source Apportionment Based on Air Modeling for Three Specific Locations in the Houston, TX Area (AECOM, 2024) (HRM = Houston Regional Monitoring)



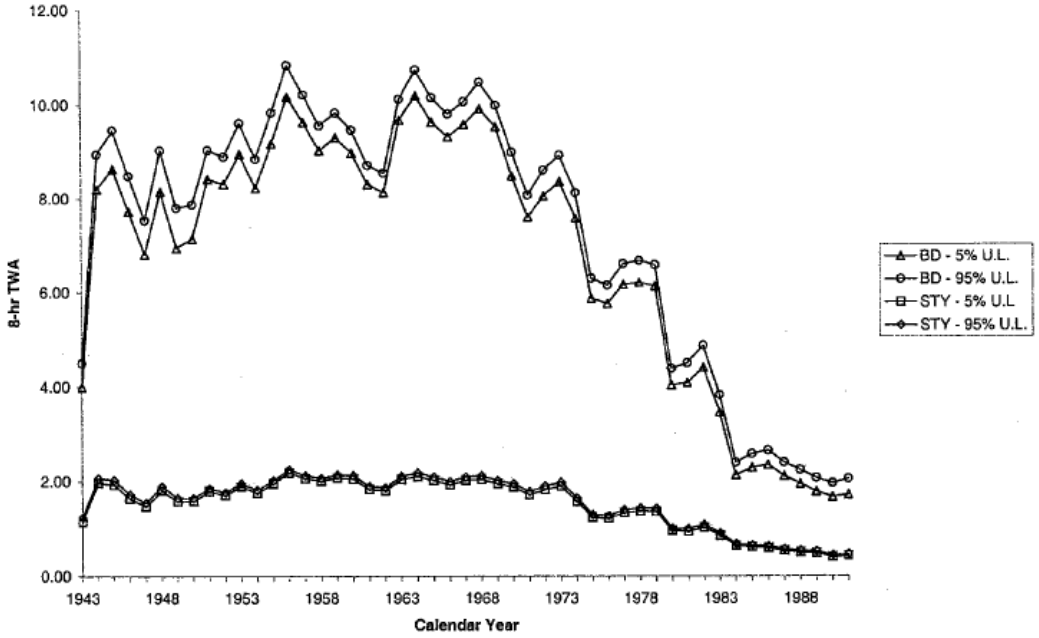
1.2.3 Exposures to BD in the U.S. Have Decreased Over Time and are Currently Low

- In addition to the decreasing trends in exposure to BD estimated from smoking noted above (**Table 1-2**), other BD exposures have generally decreased over time, including those to workers and those associated with ambient air, as summarized below.

1.2.3.1 Worker Exposures to BD Have Decreased and Are Low At Present

- In styrene-butadiene rubber (SBR) workers, BD exposures have generally decreased from the 1960s to 1991 as a result of engineering controls and regulation (in particular the establishment of Occupational Safety and Health Administration in 1970) (**Figure 1-4**).

Figure 1-4. Historical Trend for Occupational Exposure to BD (ppm) in SBR workers (Macaluso et al. 2004)



- The refined exposure estimates from Macaluso et al (2004) study shown in **Figure 1-4** serve as the exposure basis used to determine a cancer unit risk value for BD based on worker exposures and leukemia mortality (Valdez-Flores et al., 2022).
- Occupational exposures in SBR workers have continued to decrease after 1991, with current exposures to SBR workers typically being below 0.2 ppm (**Table 1-3;** IISRP, 2020)

Table 1-3. Summary of a Recent Occupational Exposure Survey for SBR Worker Exposures to BD (IISRP, 2020; rounded to two significant figures)

			Concentration (ppm)	
Activity	**Analytical Method**	**Sampling duration (range)**	**Average**	**Standard Deviation**
Analyze Samples	MDHS 88/ OSHA 7; OSHA 56	8–12 Hours	0.036	0.058
Collect samples	OSHA 56 / MDHS 88	8–12 Hours	0.012	0.021
Connecting/ Disconnecting	MDSH 88/ OSHA 56/ OSHA 7	4–8 Hours	0.0098	0.016
Maintenance Jobs	OSHA 56 / OSHA 7/ MDHS 88/ NIOSH 1024M	4–8 Hours	0.010	0.020
Routine Rounds	MDHS 88/ OSHA 7/ OSHA 56/ NIOSH 1024M	8–12 Hours	0.0087	0.017

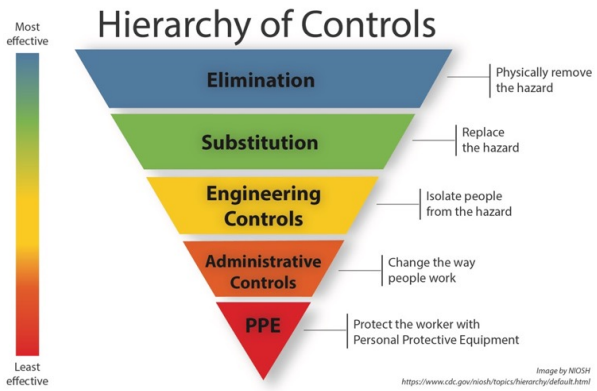
- Similarly, full-shift exposures to BD manufacturing workers are also generally below 0.5 ppm under current routine conditions (**Table 1-4;** Panko et al. 2023).

Table 1-4. Full-Shift Exposures in BD Manufacturing Workers (from Panko et al. 2023)

	N	% Non-	% DL <	Full-Shift Personal Air Concentrations (ppm)—Kaplan Meier Statistics								
Job Group	Samples	Detects	0.1 ppm	Min	50th	90th	95th	KM-Mean	SE	95LCL Mean	95UCL Mean	Max
Infrastructure/Distribution Operations	455	78%	72%	0.006	NA	0.21	0.45	0.12	0.038	0.045	0.19	16.4
Instrument and Electrical	313	91%	63%	0.008	NA	0.021	0.16	0.068	0.033	0.003	0.13	10.0
Laboratory Technician	215	73%	86%	0.006	NA	0.12	0.25	0.063	0.016	0.031	0.094	2.93
Machinery and Specialists Group	222	80%	97%	0.008	NA	0.060	0.28	0.087	0.023	0.042	0.13	3.31
Maintenance	354	69%	46%	0.001	NA	0.23	0.24	0.11	0.010	0.089	0.13	2.10
Occupational Non-User	39	77%	100%	0.008	NA	0.013	0.033	0.012	0.001	0.010	0.014	0.038
Operations Onsite	1952	88%	85%	0.0001	0.001	0.037	0.19	0.074	0.016	0.043	0.11	16.0
Safety Health and Engineering	21	71%	100%	0.038	NA	0.19	0.36	0.16	0.036	0.087	0.23	0.78
Missing Job Group Designation	378	94%	91%	0.002	NA	NA	0.037	0.024	0.004	0.016	0.032	1.3

- To reduce/minimize potential exposures to BD, facilities have implemented a hierarchy of controls that consist of elimination, substitution, engineering controls, administrative controls, and personal protective equipment (PPE) (**Figure 1-5**).

Figure 1-5. Hierarchy of Controls to Reduce/Minimize Worker Exposures



- Since 1970 OSHA has required the use of personal protective equipment (PPE) by workers when there is a reasonable probability of injury that can be prevented by such equipment. Respirator use by BD manufacturing workers has been characterized by Panko et al. (2023) (**Table 1-5**).

Table 1-5. PPE Use in BD Workers (Panko et al. 2023)

	1,3-BD Workplace air concentration ranges (ppm) reported with respirator use			
Task	Supplied Air	Full-Face APR	Half-Face APR	No Respirator
Unloading & Loading	<0.118–89	<0.06–36	<0.05–2.2	–
Handling Waste	–	<0.25–<3.7	<0.08–<0.1	–
Cleaning & Maintaining Equipment	<0.15–120	<0.02–110	<0.04–<0.7	<0.4–<0.7
Sampling Collection & Analysis	<0.52	<0.06–12	<0.09–7.3	<0.02–4.8
Performing Other Tasks	0.27–4.7	<0.24–<0.42	<0.2–<0.3	<0.39–<0.67

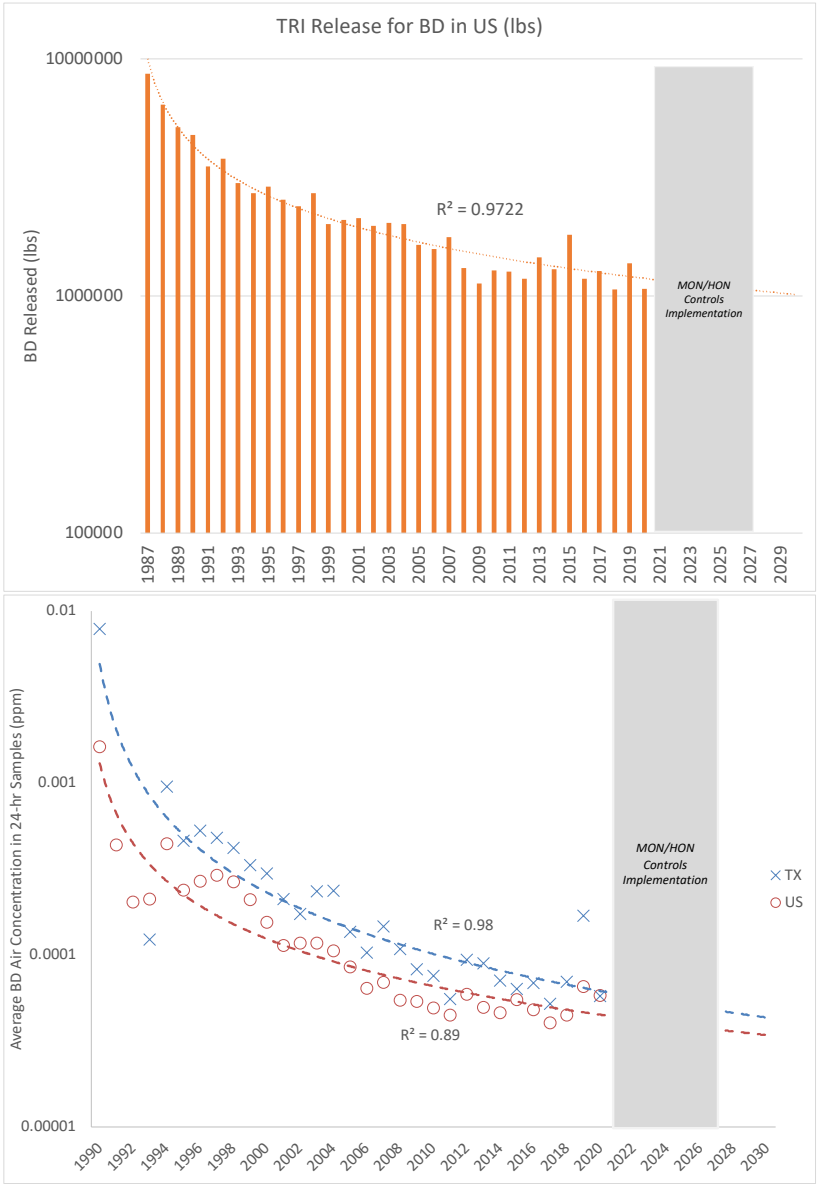
Note: APR = air-purifying respirator.

- Occupational exposures to BD for a wide variety of worker job categories in Italy have been characterized (Scarselli et al. 2017), yielding an overall mean±SD of 0.12±0.37 mg/m^3 (0.054±0.17 ppm).

1.2.3.2 Ambient Air Release and Concentrations of BD Have Decreased and Are Comparatively Low at Present

- Over the past three decades industry emissions and ambient concentrations of BD in air have been decreasing (**Figure 1-6A;** EPA TRI, 2020). National and statewide annual average levels of BD in ambient air in the U.S. and Texas are generally less than 0.0001 ppm and 0.0003 ppm, respectively, at present; **Figure 1-6B**, EPA AMA, 2020).

Figure 1-6. Historical Trends for (A) Industry BD Emissions (TRI, 2020) and (B) Concentrations in Ambient Air (EPA AMA, 2020)



- Additional decreases in emissions and resulting air concentrations of BD are expected. For example, recent regulations (EPA 2020 MON final rule; EPA 2023 HON final rule) are expected to reduce emissions of various hazardous air pollutants including BD.
- In 2020, the annual average air concentrations for BD in the US and TX were 0.000058+/-0.00014 ppm and 0.000057+/-0.00013 ppm, respectively.
- Ambient air concentrations of BD can vary from location to location depending upon proximity to important release sources (e.g., BD facilities, highways, wildfires). Measured and predicted air concentrations for several locations in the Houston, Texas near BD facilities are provided in **Table 1-5** (AECOM, 2024).

Table 1-5. Measured and Predicted BD Air Concentrations at Several Locations near Houston, Texas (AECOM, 2024)

	Annual Average (±SD) for Measured BD (ppm; reflects BD from all sources)		Predicted BD (ppm, based on industrial/petrochemical release)	
Year	**2019**	**2021**	**2019**	**2021**
Model Maximum (at facility fenceline)	NA	NA	0.00020	0.00021
HRM-3	0.000080± 0.00032	0.00013± 0.00067	0.000017	0.000013
HRM-16	0.00018± 0.0025	0.00023 0.00064	0.000022	0.000019

1.2.4. Indoor Air and In-Vehicle Air Concentrations of BD

- Huy et al. (2018) provides a comprehensive review of 1,3-butadiene concentrations in air for a variety of microenvironments. Studies that measured both indoor and outdoor air concentrations in the U.S. indicate that indoor concentrations are generally higher than outdoor. For example, average residential indoor concentrations in New York ranged from 0.00045-0.00054 ppm compared to an outdoor average concentration of 0.000045 ppm. Similarly for Los Angeles, average indoor air concentrations ranged from 0.000090-0.00022 ppm compared to outdoor average concentrations that range from 0.0000045-0.00014 ppm. Indoor air concentrations of BD are likely higher due to the contribution of a variety of indoor sources of BD (e.g., environmental tobacco smoke, wood-burning, fuel combustion/attached garages, heating some cooking oils).
- Logue et al. (2011) assembled data from seven studies that included 879 samples for BD considered to be representative of U.S. residences. These data yielded a mean indoor air concentration of 0.00021 ppm and a 95^{th} percentile of 0.00059 ppm.
- Other indoor air environments (e.g., restaurants, offices) appear to be of similar magnitude as indoor residential air (reviewed in Huy et al. 2018).
- In-vehicle air samples collected in Sacramento and Los Angeles yielded mean BD concentrations of 0.001-0.0013 ppm, and similar to levels reported in vehicles for other countries (reviewed in Huy et al., 2018).

1.2.5 Non-Inhalation Exposures of Workers to BD are Expected to be Negligible

- Based on physical-chemical properties (e.g., boiling point of -4.5 C; **Table 1-1**) BD is expected to volatilize from water, other media, and from human skin. BD is a gas at STP, and can exist in liquid forms only under high pressure/low temperature. Exposure to liquid BD is not expected, as this would result in freeze-related damage to the skin. BD in dilute solutions would be expected to rapidly volatilize from skin.

- BD exposures to workers are expected to be limited due to a hierarchy of controls. In addition, workers currently rely on personal protective equipment (PPE) to prevent cold damage due to frostbite and this will prevent/minimize potential dermal exposures to BD. As stated in Panko et al. (2023), "*The potential dermal exposure of certain workers who may contact liquid streams with trace amounts of 1,3-BD has not been assessed quantitatively; however, streams with trace amounts of BD are likely to be hydrocarbon mixtures. Safe practices in the workplace require the use of dermal protection to prevent contact with hydrocarbon mixtures. The use of gloves that are resistant to hydrocarbons would provide sufficient protection for low concentrations of BD*."
- Historically, dermal and incidental ingestion pathways for BD have not been included in worker exposure assessments for BD. For example, Macaluso et al. (2004) focused exclusively on inhalation exposures to BD to characterize historical exposures to SBR workers (see **Figure 1-4** above), which is consistent with its chemical-physical properties. In contrast, these authors did estimate dermal co-exposures to workers for a different chemical (dimethyldithiocarbamate or DMDTC), based on a consideration of its chemical-physical properties (i.e., low vapor pressure, low volatility). Because the inhalation exposure estimates of Macaluso et al. (2004) for BD have been used by agencies and risk assessors to characterize the cancer potency of BD, all dependent toxicity values (e.g., cancer unit risk values) are exclusively based on inhalation exposure estimates. For this reason, any future risk assessments for BD workers that consider contributions from dermal or incidental ingestion exposure pathways would create a problematic, inequitable treatment of BD exposures (i.e., to avoid mischaracterization or bias in potential risk estimates, the toxicity assessment and exposure assessment components of a risk assessment should treat exposure pathways equitably).
- Due to its physical-chemical properties, toxicity studies for non-inhalation exposures to BD (ingestion, dermal) are generally not available for this chemical (ATSDR, 2012) (i.e., there are no reliable toxicity studies to which worker oral and/or dermal exposure estimates could be assessed).

1.2.6 Non-Inhalation Exposures of the General Public to BD from Other Sources (Food, Water, Consumer Products) Are Expected to be Negligible

- BD Detection in Water:
  - Based on physical-chemical properties (e.g., boiling point of -4.5 C, low water solubility; **Table 1-1**), significant concentrations of BD in water are not expected to occur.
  - BD was rarely detected (1/204) in industry-impacted surface water samples in the 1970s (EPA, 1977). No recent data are available to indicate BD is detected in surface or groundwater at meaningful frequencies or concentrations (ATSDR, 2012).
- BD Detection in and Migration from Consumer Products:
  - The Ministry of Environment and Food of Denmark (MEFD) (MEFD, 2019) recently conducted a survey of BD monomer content and migration in/from polymer-based toy materials (10 products made of ABS plastic, 2 products made

of SBC plastic). Using headspace and gas chromatography with mass selective detection low levels of BD were detected using in ABS plastic samples (mean = 0.6 ug/g) and were below the limit of detection for SBC samples (<0.1 mg/kg) (**Table 1-6**). However, migrations studies using multiple simulant solutions (including 20% ethanol, artificial saliva, artificial sweat, 0.07 mol/L HCl) for all samples failed to find any concentrations above the limit of detection (<0.01 mg/L), indicating that the low levels of BD detected in plastic are not bioavailable. MEFD assessed the detection limits of their study and concluded there is no risk related to playing with toys containing BD. Based on this study, the mouthing of plastic toys is considered an incomplete pathway for BD.

Table 1-6. Residual and Migration of BD Monomer from Plastic Toys as Determined by the Ministry of Environment and Food of Denmark (MEFD, 2019).

	Residual BD Monomer			Migration of BD Monomer						
Material	**Samples**	**Measured Mean (Range), mg/kg**	**Range Reported in Other Studies, mg/kg**	**Samples (residual monomer)**	**20 % ethanol 30 minutes at 40°C Stirring**	**Artificial saliva 3 hours at 37°C Stirring**	**Artificial sweat 8 hours at 37°C Static**	**Demineralized water 3 hours at 37°C Static**	**According EN 71-3: Migration to 0.07 mol/L HCl**	**Risk-Based Level for Migration Potential**
ABS	10	0.6 (0.23 - 1.55)	<0.01-5	2 (0.35-1.55 mg/kg)	ND (<0.01 mg/L)	ND (<0.01 mg/L)	ND (<0.01 mg/L)	ND (<0.01 mg/L)	ND (<0.01 mg/L)	0.072 mg/L
SBC	2	0.13 (<0.1-0.2)	--	--	--	--	--	--	--	
SBS	--	--	<0.1	--	--	--	--	--	--	

-- = not tested/reported; ABS = acrylonitrile-butadiene-styrene; SBC = styrene-butadiene block copolymer; SBS = styrene-butadiene-styrene

- EPA (2019) assessed the emissions of BD from recycled tire crumb rubber using GC-MS. At 25 degrees C, BD emissions were below the limit of detection [not reported, but below the lowest reported value of 0.094 ng/g/h] in 27 samples of tire crumb rubber from recycling plants, and low emissions of BD were detected in 13/38 samples of tire crumb rubber from synthetic turf fields (mean below the limit of detection; maximum = 0.23 ng/g/hr). At 60 degrees C, BD emissions were again below the limit of detection [not reported, but below the lowest reported value of 0.12 ng/g/h] in 27 samples of tire crumb rubber from recycling plants, and low emissions of BD were detected in 11/37 samples of tire crumb rubber from synthetic turf fields (mean below the limit of detection; maximum = 0.81 ng/g/hr). Overall, EPA concluded that BD measurements were above quantifiable limits in only a few samples and the emission factors were low for these few samples ($\leqslant$1.0 ng/g/h). As such, BD release from tires is not expected to serve as an important source to BD in air, and to the extent there are releases they are expected to be reflected in available air monitoring data for BD (**Figure 1-5**).

- Residual monomer data for BD reported in unpublished data continue to show that the levels of BD in materials are very low: mean < 0.05 mg/kg for various synthetic rubbers (**Table 1-7**).
- A separate white paper has been prepared that summarizes available information on residual BD monomer (unpublished white paper: *Residual Butadiene in BD-derived polymers and resins – Summary of the evidence*)

Table 1-7. Survey Results for Residual BD Monomer in Rubber (conducted in the first Quarter 2020 in the US; IISRP, 2020)

Product	Residual BD	Unit	Method, remarks
ESBR	<50	ppb	Head Space-Gas Chromatography /Mass Spectrometry Method
SSBR	<20	ppb	GC/MS Method
SBS	ND	ppb	GC/MS Method and EPA Method 8260
BR	<20	ppb	GC/MS Method
SEBS	ND	ppb	GC/MS Method

- Limits for residual BD monomer in consumer products include the following:
  - In 2011, EU established a limit of 1 mg/kg in final product for residual BD monomer (and for several other monomers) for materials used for food contact purposes (EU, 2011).
  - A limit of 1 mg/kg has been proposed for residual BD in toys, and is applicable for toys intended for use by children below 3 years and for toys which are intended to be placed in the mouth (ANEC, 2018).
  - MEFD (2019) defined a risk-based migration limit of 0.072 mg/L for BD in simulated biological fluids (saliva, sweat, gastric) to be protective of exposures to children (**Table 1-6**). ABS samples containing 0.35-1.55 mg/kg BD monomer yielded migration measurements that were below the limit of detection (0.01 mg/L), which in turn is more than 7-fold below this risk-based level.

<u>Authoritative Body Conclusions on the Importance of BD Exposures Via Non-Inhalation Pathways</u>

- Health agencies have historically considered non-inhalation exposure pathways to be negligible for BD:
  - Health Canada (2000): "*Although few data were identified regarding levels in drinking water and food, intake of butadiene in these media is expected to be negligible in comparison with that in air because of its physical/chemical properties (e.g., vapour pressure and partition coefficients) and environmental release patterns (i.e., principally atmospheric emissions).*"

- WHO. (2001): "*The general population is exposed to 1,3-butadiene primarily through ambient and indoor air. In comparison, other media, including food and drinking-water, contribute negligibly to exposure to 1,3-butadiene.*"
- EPA IRIS (2002): "*The hazard by ingestion is unlikely since 1,3-butadiene is poorly soluble in water. When released in water, 1,3-butadiene rapidly evaporates.*"
- ATSDR (2012): "*The available data indicate that exposure to 1,3-butadiene through ingestion of food and drinking water is expected to be low relative to inhalation exposure*."
- ECHA (2014): *"...the exposures arising as a result of potential release of monomeric 1,3-butadiene from consumer products give rise to very low doses. The risks to human health under current consumer exposure levels are uncertain, but in view of the very low estimated exposure levels, it is predicted that there would be negligible residual risk.*"
- ECHA (2014): "*It is expected that any 1,3-butadiene present in surface water will volatilise rapidly. Therefore, even if 1,3-butadiene is released to surface water from point sources, the concentration would be expected to decrease markedly with increasing distance from the source.*"
- ECHA (2023): *"The potential for oral or dermal exposure cannot be entirely excluded but is considered to represent a very minor route of exposure in comparison to inhalation."*

1.2.7 Exposure Summary and Conclusions

Based on the data summarized above, the following "strawman" position statements are proposed to help guide the human health risk assessment for BD:

1. *Inhalation is primary route of exposure for BD, and should serve as the focus of efforts to quantify potential hazards and risks to human health*
2. *Important exposure sources for BD in air include indoor air (occupational, residential), ambient air, in-vehicle air, and smoking*
3. *The following exposure pathways are considered to be either incomplete or negligible compared to inhalation. As such, these pathways do not require quantification in risk assessment (but could be discussed qualitatively or semi-quantitatively).*
    a. *Ingestion water containing BD*
    b. *Dermal contact with BD (pure liquid and/or dilute solutions)*
    c. *Migration of BD from polymers used in consumer products (e.g., toys, tires)*

A draft exposure pathway summary for BD is provided in **Table 1-8.**

399 **Table 1-8. Proposed Exposure Pathways for Human Health Risk Assessment of BD**

400

Life Cycle Stage / Exposure Category	Receptor	Exposure Scenario(s)	Exposure Media	Exposure Route	Evaluation in Risk Assessment	Rationale for Further Evaluation / no Further Evaluation
Manufacture	Manufacturing Workers	- Instrument and Electrical - Laboratory Technician - Machinery and Specialists Group - Maintenance - Operations Onsite - Safety Health and Engineering - Missing Job Group Designation - Occupational Non-User	Workplace Air	Inhalation	Yes (quantitative)	Comprehensive IH data available (**Table 4**; Panko et al. 2023). The effect of PPE on exposure estimates should be considered.
				Dermal vapor	No	The dermal absorption of BD vapor is expected to be orders of magnitude lower than corresponding inhalation exposures. The dermal vapor pathway has not been explicitly assessed for worker exposures used to characterized BD cancer and noncancer potency.
			Liquid	Dermal contact	No	Due to engineering controls and use of PPE, dermal exposures are not expected to occur. Due to physical-chemical properties (e.g., boiling point of -4.5 C), rate of volatilization from skin is expected to far exceed rate of absorption. The dermal vapor pathway has been ignored for the worker exposures used to characterized BD cancer and noncancer potency.
Industrial Use	SBR Workers	- Analyze samples - Collect samples - Connecting/Disconnecting - Maintenance Jobs - Routine Rounds	Workplace Air	Inhalation	Yes (quantitative)	Limited IH data are available for SBR workers (**Table 3**; IISRP, 2020). The effect of PPE on exposure estimates should be considered.
				Dermal vapor	No	The dermal absorption of BD vapor is expected to be orders of magnitude lower than corresponding inhalation exposures. The dermal vapor pathway has not been explicitly assessed for worker exposures used to characterized BD cancer and noncancer potency.
			Liquid	Dermal contact	No	Due to engineering controls and use of PPE, dermal exposures are not expected to occur. Due to physical-chemical properties (e.g., boiling point of -4.5 C), rate of volatilization from skin is expected to far exceed rate of absorption. The dermal liquid pathway has been ignored for the worker exposures used to characterized BD cancer and noncancer potency.
	Other Downstream Users	From EPA (2020): Adhesives and Sealants (epoxy resins) Automotive Care Products Fuel and Related Products	Workplace Air	Inhalation	Yes (quantitative)	Occupational exposures to BD for a wide variety of job categories have been characterized in Italy (Scarselli et al. 2017).

		Laboratory Chemicals Paints and Coatings Processing aids specific to petroleum production (e.g. hydraulic fracturing fluid)		Dermal vapor	No	The dermal absorption of BD vapor is expected to be orders of magnitude lower than corresponding inhalation exposures. The dermal vapor pathway has not been explicitly assessed for worker exposures used to characterized BD cancer and noncancer potency.
			Liquid	Dermal contact	No	Due to engineering controls and use of PPE, dermal exposures are not expected to occur. Due to physical-chemical properties (e.g., boiling point of -4.5 C), rate of volatilization from skin is expected to far exceed rate of absorption. The dermal liquid pathway has been ignored for the worker exposures used to characterized BD cancer and noncancer potency.
Offsite Release from Facilities	General Public	General Public	Ambient Air	Inhalation	Yes (quantitative)	Ambient air monitoring (EPA AMA, 2020) and air modeling data near industrial facilities are available (AECOM, 2024); Contributions from nonindustrial releases are important and should also be considered
Consumer Products			Consumer Goods/Food Packaging	Ingestion	No	Levels of residual monomer in consumer goods (plastic, rubber products) are either low or below limits of detection. Detectable levels do not migrate and therefore are not considered to be bioavailable (see **Table 6**). Agencies have historically considered non-inhalation pathways to be negligible (see Section 2.6)
Other Sources			Indoor Air	Inhalation	Yes (quantitative)	Publications on indoor air levels of BD are available (reviewed in Huy et al., 2018; Logue et al. 2011)
			In-vehicle Air	Inhalation	Yes (quantitative)	Publications on in-vehicle air levels of BD are available (reviewed in Huy et al., 2018)
			Smoking	Inhalation	Yes (semi-quantitative)	Biomonitoring data for the U.S. population can be used to make relative comparisons between smokers and nonsmokers (Nieto et al. 2021)

401 Shaded regions indicate exposure pathways that are considered to be incomplete or negligible.

1.3. BD Toxicity Values Derived by Authoritative Bodies

- USEPA's assessment for BD (EPA, 2002) is more than twenty years old.
- USEPA, like most agencies and assessors, derived noncancer values based on fetal body weight changes and ovarian atrophy from studies in laboratory rodents, and derived cancer values based on leukemia in styrene-butadiene rubber (SBR) workers (**Table 1-9**).
    - At the time these assessments were prepared there were insufficient data to quantify species differences in the metabolic activation of BD, resulting in the use of conservative assumptions for interspecies extrapolation.
- Over the past two decades, two areas of research have greatly improved our understanding of BD's toxicity and carcinogenicity.
    - Based on robust data on metabolite-specific biomarkers (Swenberg et al. 2007, 2011; Georgieva et al. 2010; Boysen et al. 2012), we now have a much better understanding of the large species differences in metabolic activation that underly species differences in BD's potency. These data have been used to support an approach for interspecies extrapolation for risk assessment (Motwani and Tornqvist, 2014). This research is not controversial. Because of these species differences ATSDR (2012, Section 2.3) decided to not adopt the conservative assumptions for BD, and therefore did not derive Minimal Risk Levels (MRLs) out of concern for overestimating potential risks to humans.
    - The SBR cohort has undergone multiple updates, most recently in 2021 (Sathiakumar et al. 2021a,b), and now includes more years of follow-up, refined exposure estimates, and data for female workers (see Table 1 from Valdez-Flores et al., 2022).

Table 1-9. Summary of Available Agency Assessments for BD

Assessor (Year)	Assessment	Endpoint	Data set	Toxicity Value	Note
Health Canada (2000)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	LEC05 = 0.44 mg/m^3	Interspecies extrapolation approach is outdated
	Cancer	Leukemia	SBR workers (Delzell et al. 1995)	TC01 = 1.7 mg/m^3	Cohort and exposures are not current
USEPA (2002)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	RfCc = 0.9 ppb	Interspecies extrapolation approach is outdated
	Acute & Subchronic Noncancer	Fetal body weight	Mice (Hackett et al. 1987)	RfCs = 7 ppb	Interspecies extrapolation approach is outdated
	Cancer	Leukemia	SBR workers (Delzell et al. 1995)	0.08 (ppm-1)	Cohort and exposures are not current
ATSDR (2012)	Acute, Intermediate, Chronic Minimal Risk Levels (MRLs)	ATSDR elected to not derive acute-, intermediate-, and chronic-duration inhalation minimal risk levels for BD due to the lack of chemical-specific data to adjust for the large species differences in metabolism, which may result in the MRL overestimating the risk to humans			

OEHHA (2013)	Acute Reference Exposure Level (REL)	Fetal body weight	Mice (Hackett et al., 1987; as reanalyzed by Green, 2003)	297 ppb	Interspecies extrapolation approach is outdated
	8-Hours REL	Ovarian atrophy	Female mice (NTP, 1993; Doerr et al., 1996)	4 ppb	Interspecies extrapolation approach is outdated
	Chronic REL	Ovarian atrophy	Female mice (NTP, 1993)	1 ppb	Interspecies extrapolation approach is outdated
	Inhalation unit risk (NSRL basis)	Multiple tumors	Mice (NTP, 1984; Melnick et al. 1990)	0.00017 (ug/m3)-1	Interspecies extrapolation approach is outdated
TCEQ (2015)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	15 ppb	Interspecies extrapolation approach is outdated
	Acute Noncancer	Fetal body weight	Mice (Hackett et al. 1987)	430 ppb (24-hr)	Interspecies extrapolation approach is outdated
	Chronic cancer inhalation unit risk	Leukemia	SBR workers (Sathiakumar and Delzell, 2009)	5.0E-07 per µg/m3 (1.1E-06 per ppb)	Cohort is not current

- Because the assessments listed in **Table 1-8** do not reflect the scientific weight of evidence, they are not recommended for use in human health risk assessment of BD exposures under TSCA.
- A literature search was conducted to identify additional endpoints/studies that could serve as the bases for the noncancer and cancer risk assessment for BD (see **Attachment 1** of **Appendix A**). As noted above, the SBR cohort has been updated (Sathiakumar et al., 2021a,b), and is considered the best available data for assessing cancer endpoints. No additional rodent cancer bioassays were identified. For the noncancer assessment, no additional studies or endpoints were identified to supercede the selection of fetal body weight changes and ovarian atrophy as the bases for risk assessment.

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2. Review Material for Round 3

2.1. Introduction

The text below summarizes the equations and parameter values proposed for quantifying exposures, noncancer hazards, and cancer risks to human populations exposed to 1,3-butadiene (BD).

Noncancer Hazard

$$HQ = HE / RfC \quad \text{Eq.1}$$

$$MOE = \text{Noncancer POD} / HE \quad \text{Eq.2}$$

Where:

- HQ = Noncancer hazard quotient (unitless);
- HE = Human exposure (ppm, continuous exposure);
- RfC = Reference concentration (ppm, continuous); Calculated as (Noncancer POD) / (Net uncertainty factor value);
- MOE = Margin of exposure (unitless); and
- Noncancer POD = Point of departure for key noncancer endpoint (human equivalent concentration, ppm continuous).

Cancer Risk

$$CR = HE \times IUR \quad \text{Eq.3}$$

Where:

- CR = Extra cancer risk (unitless);
- HE = Human exposure (lifetime average daily concentration, ppm continuous); and
- IUR = Inhalation unit risk (extra risk per ppm); calculated as (Benchmark response rate or BMR) / (Point of departure or POD).

Human Exposure (HE)

$$HE_{(NC\ or\ C)} = (C \times BR \times ET \times EF \times ED) / (AT_{(NC\ or\ C)} \times PF) \quad \text{Eq.4}$$

Where:

- HE = Human exposure (duration-specific average daily concentration or lifetime average daily concentration, ppm continuous);
- PF = Protection factor offered by the use of personal protective equipment (applied to worker exposures only; for general population scenarios PF will be excluded from the calculations);
- BR = Breathing rate ratio (unitless);
- ET = Exposure time (hours/day);
- EF = Exposure frequency (days/year or days/month depending upon duration);

- ED = Exposure duration (years); and
- $AT_{(NC\ or\ C)}$ = Averaging time; for noncancer hazard AT will be calculated as 24 hours/day x (30 days/month or 365 days/year) x ED; for cancer risk AT will be calculated as 24 hours/day x (30 days/month or 365 days/year) x Lifetime (e.g., 78 years)

For any potential acute assessments, a simplified version of Eq. 4 may be used (e.g., elimination of terms for EF and ED).

For the human health risk assessment of BD, probabilistic methods (i.e., 1-dimensional Monte Carlo simulations) will be used to characterize sources of variation and/or uncertainty in the parameter values used to quantify hazards and risks for the inhalation pathway. The text below summarizes the information proposed to be used to define distributions for the parameters needed in Eq. 1-4.

2.2. Exposure Parameter Values

2.2.1 Concentrations for BD in Air: C (ppm)

- For characterization of exposures to BD manufacturing workers, the data of Panko et al. (2023) are considered to be robust (**Table 2-1**), and are proposed to serve as the primary basis to define distributions for the concentration of BD in workplace air.

Table 2-1. BD Concentrations in Workplace Air of BD Manufacturing Workers (Panko et al. 2023): (A) Full-shift personal air samples – routine operations; (B) Short-term and task personal air samples – routine operations

(A)

				Full-Shift Personal Air Concentrations (ppm)—Kaplan Meier Statistics							
Job Group	N Samples	% Non-Detects	% DL < 0.1 ppm	Min	50th	90th	95th	KM-Mean	SE	95LCL Mean	95UCL Mean
Infrastructure/Distribution Operations	455	78%	72%	0.006	NA	0.21	0.45	0.12	0.038	0.045	0.19
Instrument and Electrical	313	91%	63%	0.008	NA	0.021	0.16	0.068	0.033	0.003	0.13
Laboratory Technician	215	73%	86%	0.006	NA	0.12	0.25	0.063	0.016	0.031	0.094
Machinery and Specialists Group	222	80%	97%	0.008	NA	0.060	0.28	0.087	0.023	0.042	0.13
Maintenance	354	69%	46%	0.001	NA	0.23	0.24	0.11	0.010	0.089	0.13
Occupational Non-User	39	77%	100%	0.008	NA	0.013	0.033	0.012	0.001	0.010	0.014
Operations Onsite	1952	88%	85%	0.0001	0.001	0.037	0.19	0.074	0.016	0.043	0.11
Safety Health and Engineering	21	71%	100%	0.038	NA	0.19	0.36	0.16	0.036	0.087	0.23
Missing Job Group Designation	378	94%	91%	0.002	NA	NA	0.037	0.024	0.004	0.016	0.032

(B)

				Short-Term Personal Air Concentrations (ppm)—Kaplan Meier Statisti							
Task Code	Sample Duration (minutes)	N Samples	% Non-Detects	Min	50th	90th	95th	KM-Mean	SE	95LCL Mean	95UCL Mean
Unloading & Loading	<=15	89	45	0.04	1.0	8.1	17	2.7	0.52	1.7	3.7
	>15	158	45	0.02	0.73	8.0	18	3.6	0.77	2.1	5.1
Handling Waste	<=15	7	100	0.06	NA	NA	NA	NA	NA	NA	NA
	>15	10	90	0.08	NA	0.69	0.69	0.69	NA	NA	NA
Cleaning & Maintaining	<=15	102	80	0.06	NA	2.7	15	3.9	1.4	1.1	6.7
Equipment	>15	159	73	0.02	0.06	2.6	8.3	1.8	0.77	0.28	3.3
Sample Collection & Analysis	<=15	187	89	0.03	NA	0.51	1.3	0.52	0.04	0.44	0.59
	>15	237	89	0.02	NA	0.36	2.10	0.49	0.12	0.25	0.74
Performing Other Tasks	<=15	31	71	0.2	0.20	0.54	2.1	0.49	0.22	0.06	0.92
	>15	21	81	0.02	NA	0.17	3.7	0.49	0.31	−0.11	1.1

- For downstream workers (i.e., those that use BD or BD-containing materials), available data to characterize exposure to styrene-butadiene rubber (SBR) workers is based on summary statistics provided by IISRP from a survey conducrted in 2020 (**Table 2-2**) . Because information regarding the number of samples collected is not available in this the summary, standard errors for the reported mean values could not be calculated. The

U.S. Tire Manufacturers Association reported BD air samples for three companies from 1998-2018 that reflect exposures to workers and occupational non-users (ONU) (**Table 2-3**).

Table 2-2. BD Concentrations in Workplace Air of Styrene-Butadiene Rubber Workers (IISRP, 2020)

			Air Concentration (ppm)	
Activity	**Analytical Method**	**Sampling duration (range)**	**Average**	**Standard Deviation**
Analyze Samples	MDHS 88/ OSHA 7; OSHA 56	8 –12 Hours	0.0359	0.0576
Collect samples	OSHA 56 / MDHS 88	8 –12 Hours	0.0124	0.0209
Connecting/ Disconnecting	MDSH 88/ OSHA 56/ OSHA 7	4 –8 Hours	0.0098	0.0157
Maintenance Jobs	OSHA 56 / OSHA 7/ MDHS 88/ NIOSH 1024M	4 –8 Hours	0.0102	0.0199
Routine Rounds	MDHS 88/ OSHA 7/ OSHA 56/ NIOSH 1024M	8 –12 Hours	0.0087	0.0174

Table 2-3. BD Concentrations in Workplace Air (8-12 hour samples) of Tire Manufacture Workers (USTMA, 2020)

			Air Concentration (ppm)*		
Exposure Category	**Number of Samples**	**Detection Frequency**	**Mean**	**SEM**	**Maximum**
Worker	87	31/87	0.091	0.011	0.475
Occupational non-user (ONU)	9	0/9	0.041**	0.0039**	0.045**

*Statistics are based on treating nondetect values using detection limit/2

**Values reflect detection limits/2 (no detected values reported for this exposure category)

- Data to support characterize other downstream workers that use BD or BD-containing materials are generally lacking (although efforts are underway to collect this information). As an alternative, BD exposures from a variety of sources (i.e., including from BD-containing materials as well as from the combustion of fuels) has been characterized in Italian workers for 46 job categories (**Table 2-4**; Scarselli et al. 2017). The concentrations reported in this study appear to be of similar magnitude when compared to those above in **Tables 2-1** through **2-3**, and therefore it is proposed that these data could be used as a surrogate to characterize U.S. worker exposures (either for specific job categories, or considered together as a whole) under an assumption that exposures in both countries are similar.

Table 2-4. BD Concentrations in Workplace Air (from a variety of sources) for Italian Workers (Scarselli et al. 2017); Data converted from mg/m^3 to ppm and sorted in descending order of mean concentration

		Air Concentration (ppm)	
Activity sector (NACE Rev 1 code) / Occupational group (ISCO-88 code)	**N**	**Mean**	**SEM**

Petroleum- and natural-gas-refining-plant operators (8155)	1475	0.18	0.012
Plastic-products machine operators (8232)	109	0.16	0.011
Manufacture of coke, refined petroleum products (23)	1698	0.15	0.011
Manufacture of rubber and plastic products (25)	136	0.14	0.010
Chemists (2113)	99	0.14	0.020
Petroleum- and natural-gas-refining-plant operators (8155)	190	0.11	0.001
Chemical-processing-plant operators n.e.c. (8159)	509	0.11	0.011
Motor vehicle mechanics and fitters (7231)	106	0.09	0.002
Electricity, gas, steam and hot water supply (40)	143	0.09	0.021
Bricklayers and stonemasons (7122)	75	0.09	0.004
Manufacture of machinery and equipment n.e.c (29).	148	0.09	0.002
Other business activities (74)	621	0.08	0.008
Construction (45)	309	0.08	0.005
Building structure cleaners (7143)	136	0.08	0.005
Sewage and refuse disposal, sanitation and similar activities (90)	1097	0.08	0.006
Chemical-processing-plant operators n.e.c. (8159)	5410	0.07	0.002
Petroleum- and natural-gas-refining-plant operators (8155)	103	0.07	0.019
Chemical-processing-plant operators n.e.c. (8159)	104	0.07	0.014
Well drillers and borers and related workers (8113)	177	0.06	0.004
Manufacture of chemicals and chemical products (24)	18744	0.04	0.001
Electronics mechanics, fitters and servicers (7242)	228	0.041	0.006
Petroleum- and natural-gas-refining-plant operators (8155)	4914	0.041	0.001
Chemists (2113)	1026	0.036	0.002
Mechanical engineers (2145)	768	0.036	0.003
Physical and engineering science technicians n.e.c. (3119)	81	0.032	0.007
Agricultural- or industrial-machinery mechanics and fitters (7233)	92	0.032	0.007
Extraction of crude petroleum and natural gas (11)	616	0.027	0.002
Mechanical engineering technicians (3115)	1000	0.027	0.002
Technical and commercial sales representatives (3415)	300	0.027	0.004
Stock clerks (4131)	742	0.027	0.002
Electrical engineers (2143)	135	0.023	0.004
Chemical and physical science technicians (3111)	208	0.023	0.006
Electrical engineering technicians (3113)	725	0.023	0.002
Safety, health and quality inspectors (3152)	428	0.018	0.002
Fire-fighters (5161)	427	0.018	0.002
Power-production plant operators (8161)	560	0.018	0.001
Petroleum- and natural-gas-refining-plant operators (8155)	222	0.014	0.002
Research and development managers (1237)	485	0.014	0.002
Trade brokers (3421)	114	0.014	0.002
Manufacture of motor vehicles, trailers and semi-trailers (34)	181	0.009	0.001
Mechanical engineers (2145)	78	0.005	0.001

Chemical-processing-plant operators NEC (8159)	179	0.005	0.002
Chemical engineers (2146)	176	0.005	0.004
Motor vehicle mechanics and fitters (7231)	75	0.005	0.001
Incinerator, water-treatment and related plant operators (8163)	213	0.005	0.0003
Plastic-products machine operators (8232)	107	0.001	0.0004
Overall	***26725***	***0.054***	***0.00078***

- For characterization of ambient air exposures to BD at the national, state, and local levels, air monitoring data from USEPA are available (**Table 2-5**). For characterization of local air concentrations, a BD facility in Houston, TX was selected as an upper-bound characterization. Specifically, this site ranks in the 91%-ile for the FUGITIVE-AIR category, and 98%-ile for the STACK-AIR category for the U.S. (and the 83%-ile and 95%-ile, respectively, for Texas) (AECOM, personal communication). It is important to note that air monitoring data reflect BD from a variety of sources (i.e., see summary report provided for Round 1 of this review); whereas the air modeling data for BD reflect only site-related releases. Additional characterization (geospatial variation near a BD facility) will rely upon a recent air modeling report for site-specific releases (**Table 2-5**; AECOM, 2024).

Table 2-5. Annual Average BD Concentrations in Ambient Air (USEPA AMA 2020; AECOM, 2024)

		Air Concentration (ppm)		
Ambient Scenario	**Description**	**Average**	**SEM**	**Reference**
National	24-hour average concentration of BD based upon air monitoring locations across the U.S. in 2020 (reflects multiple sources)	0.000058	0.000012	USEPA AMA 2020
State	24-hour average concentration of BD based upon air monitoring locations across Texas in 2020 (reflects multiple sources)	0.000057	0.000023	USEPA AMA 2020
Local	24-hour average concentration of BD based upon air monitoring data for station HRM-16 near a	0.00023	0.000019	AECOM (2024)

	BD facility in Houston, TX in 2021 (reflects multiple sources)			
	24-hour average concentration of BD based upon air modeling predictions near BD facility in Houston, TX (reflects site-related releases)	0.000022	Modeling predictions for each gridpoint are available to characterize geospatial variation around the facility	AECOM (2024)

NA = not available; NR = not reported

- Information on the concentration of BD in indoor air is summarized in **Table 2-6**. Studies that measured both indoor and outdoor air concentrations in the U.S. indicate that indoor concentrations are generally higher than outdoor (Huy et al. 2018). Indoor air concentrations of BD are likely higher due to the contribution of a variety of indoor sources of BD (e.g., environmental tobacco smoke, wood-burning, fuel combustion/attached garages, heating some cooking oils).For the quantitative risk assessment, the data compiled by Logue et al. (2011) across multiple studies are proposed to serve as the primary basis for defining a distribution of indoor air concentrations of BD.

Table 2-6. BD Concentrations in Indoor Air (Huy et al. 2018; Logue et al. 2011)

		Concentration (ppm)			
Country	**City**	**Average**	**SD**	**Maximum**	**Source**
United States	New York, winter	0.00045	0.00063	0.00262	see Table 3 of Huy et al. (2018) for specific references
	New York, summer	0.00054	0.00118	0.00542	
	Los Angeles, winter	0.00023	0.00027	0.00081	
	Los Angeles, summer	0.00009	0.00014	0.00068	
Canada	--	0.000054	NR	NR	
United Kingdom	Multiple cities	0.00011	0.00014	0.00092	
	Birmingham	0.00050	0.00086	0.00488	
Sweden	Hagfors	0.00014	NR	NR	
		0.000050	NR	NR	
China	Tianjin	0.00024	0.00014	0.00000	
Mexico	Mexico City	0.00113	0.00095	0.00375	
United States	Multiple cities (879 samples across 7 studies either from or considered representative of the US)	0.00021	NR	0.00059*	Logue et al. (2011; Supplement)

NR = not reported

*95th percentile (maximum not reported)

- Information on the concentration of BD present in air inside of vehicles is summarized in **Table 2-7**. These levels are attributed to fuel combustion since BD was reportedly only observed at significant concentrations inside the cabins of moving vehicles during peak-hour traffic, otherwise in-vehicle levels were near ambient levels and/or the detection limit (Duffy and Nelson, 1997). For the quantitative risk assessment, a distribution based on a pooled data set across studies is proposed.

Table 2-7. BD Concentrations in In-Vehicle Air (see Table 4 of Huy et al. 2018 for specific references)

		Air Concentration (ppm)		
Country	**City**	**Average**	**SD**	**Maximum**
United States	Sacramento	0.00102	NR	0.00158
	Los Angeles	0.00133	NR	0.00167

United Kingdom	Multiple	0.000059	0.00164	NR
	Birmingham	0.00160	NR	NR
Sweden	NR	0.00024	NR	0.00041
China	Tianjin	0.00028	0.00015	NR
Ireland	Dublin	0.00066	0.00041	NR
		0.00078	0.00034	0.00149

2.2 Inhalation Rates (BR)

- For many scenarios use of default breathing ratio (BR) of 1 will be appropriate for use in Eq.4, in which case variation in inhalation rates will not need to be considered. However, in some cases, differences in inhalation rates for specific subpopulations (as compared to the general population) may need to be considered in the risk assessment using the BR term defined in Eq. 4. For the assessment of the fetal body weight changes of BD is may be important to address the increase in inhalation rates during pregnancy (**Table 2-8**). These data may be used to develop a duration-specific distribution for inhalation rate.

Table 2-8. Inhalation Rates for Pregnant Women (USEPA EFH 2011; from Table 6-54)

Age Group (years)	Progression of the Reproductive Cycle	Number of Subjects[b] NExp or NSim	Physiological Daily Inhalation Rates[c] (m^3/day)								
			Percentile								
			Mean ± SD	5th	10th	25th	50th	75th	90th	95th	99th
11 to <23	Non-pregnant females	57	14.55 ± 2.70	10.11	11.09	12.73	14.55	16.37	18.01	18.99	20.83
	Pre-pregnancy 0 week	5,000	14.55 ± 2.69	9.71	10.83	13.29	14.78	15.89	17.34	18.71	20.91
	Pregnancy 9th week	5,000	19.99 ± 3.89	13.32	14.84	18.32	20.26	21.86	23.86	25.89	28.75
	Pregnancy 22nd week	5,000	22.59 ± 4.83	15.35	17.09	20.06	22.27	24.69	28.25	30.75	35.88
	Pregnancy 36th week	5,000	23.27 ± 4.63	16.01	17.76	20.69	23.10	25.55	28.77	31.07	35.65
	Postpartum 6th week	5,000	23.28 ± 3.60	16.91	18.36	21.40	23.56	25.24	27.17	28.98	31.80
	Postpartum 27th week	5,000	23.08 ± 3.56	16.76	18.20	21.21	23.36	25.02	26.93	28.73	31.52
23 to <30	Non-pregnant females	54	13.59 ± 2.23	9.92	10.73	12.09	13.59	15.09	16.45	17.26	18.78
	Pre-pregnancy 0 week	5,000	13.66 ± 2.29	10.19	10.64	12.12	13.73	14.90	16.49	17.87	19.09
	Pregnancy 9th week	5,000	19.00 ± 9.98	13.92	14.55	16.55	18.76	20.49	22.80	24.49	27.04
	Pregnancy 22nd week	5,000	21.36 ± 4.36	15.54	16.70	18.63	20.89	23.58	26.59	28.43	33.98
	Pregnancy 36th week	5,000	22.14 ± 4.13	16.21	17.34	19.35	21.69	24.55	27.59	29.27	32.77
	Postpartum 6th week	5,000	22.15 ± 30.5	17.37	18.26	20.11	22.11	23.96	26.21	27.53	29.21
	Postpartum 27th week	5,000	21.96 ± 3.02	17.22	18.10	19.93	21.91	23.75	25.98	27.29	28.96
30 to 55	Non-pregnant females	61	13.82 ± 1.91	10.67	11.37	12.53	13.82	15.12	16.28	16.97	18.28
	Pre-pregnancy 0 week	5,000	13.79 ± 1.83	11.07	11.48	12.54	13.61	14.91	16.40	17.02	18.32
	Pregnancy 9th week	5,000	19.02 ± 3.81	15.18	15.74	17.14	18.63	20.46	22.45	23.38	27.39
	Pregnancy 22nd week	5,000	21.53 ± 4.06	16.71	17.56	19.01	20.85	23.45	26.03	28.30	33.44
	Pregnancy 36th week	5,000	22.20 ± 3.68	17.45	18.19	19.69	21.73	24.16	26.78	28.53	32.75
	Postpartum 6th week	5,000	22.31 ± 2.50	18.72	19.35	20.58	22.09	23.84	25.70	26.70	28.39
	Postpartum 27th week	5,000	22.12 ± 2.48	18.55	19.18	20.40	21.90	23.64	25.47	26.47	28.14

[a] Normal-weight females are defined as those having a body mass index varying between 19.8 and 26 kg/m^2 in pre-pregnancy.
[b] NExp = number of experimental non-pregnant and non-lactating females; NSim = number of simulated females.
[c] Resulting TDERs from the integration of energetic measurements in underweight non-pregnant and non-lactating females with those during pregnancy and lactation by Monte Carlo simulations were converted into physiological daily inhalation rates by the following equation: $TDER \times H \times (V_E/VO_2) \times 10^{-3}$. *TDER* = total energy requirement (*ECG* + *TDEE*). *ECG* = stored daily energy cost for growth; *TDEE* = total daily energy.
SD = Standard deviation.
Source: Brochu et al. (2006a).

- In cases where default inhalation rates are not appropriate, age- and duration-specific inhalation rates for the general population may be defined based upon the information provided in **Table 2-9**. For assessment of ovarian atrophy, inhalation rate distributions may be defined based on inhalation rates in women up through menopause. For assessment of cancer risks, inhalation rate distributions may be defined based on inhalation rates for men and women combined.

Table 2-9. Inhalation Rates for Men and Women as a Function of Age (USEPA EFH 2011; from Table 6-4)

Age Group (years)	N	Body Weight[a] (kg) Mean ± SD	Physiological Daily Inhalation Rates[b] (m^3/day) Mean ± SD	Percentile[c] 5th	10th	25th	50th	75th	90th	95th	99th
Males											
0.22 to <0.5	32	6.7 ± 1.0	3.38 ± 0.72	2.19	2.46	2.89	3.38	3.87	4.30	4.57	5.06
0.5 to <1	40	8.8 ± 1.1	4.22 ± 0.79	2.92	3.21	3.69	4.22	4.75	5.23	5.51	6.05
1 to <2	35	10.6 ± 1.1	5.12 ± 0.88	3.68	3.99	4.53	5.12	5.71	6.25	6.56	7.16
2 to <5	25	15.3 ± 3.4	7.60 ± 1.28	5.49	5.95	6.73	7.60	8.47	9.25	9.71	10.59
5 to <7	96	19.8 ± 2.1	8.64 ± 1.23	6.61	7.06	7.81	8.64	9.47	10.21	10.66	11.50
7 to <11	38	28.9 ± 5.6	10.59 ± 1.99	7.32	8.04	9.25	10.59	11.94	13.14	13.87	15.22
11 to <23	30	58.6 ± 13.9	17.23 ± 3.67	11.19	12.53	14.75	17.23	19.70	21.93	23.26	25.76
23 to <30	34	70.9 ± 6.5	17.48 ± 2.81	12.86	13.88	15.59	17.48	19.38	21.08	22.11	24.02
30 to <40	41	71.5 ± 6.8	16.88 ± 2.50	12.77	13.68	15.20	16.88	18.57	20.09	21.00	22.70
40 to <65	33	71.1 ± 7.2	16.24 ± 2.67	11.84	12.81	14.44	16.24	18.04	19.67	20.64	22.46
65 to ≤96	50	68.9 ± 6.7	12.96 ± 2.48	8.89	9.79	11.29	12.96	14.63	16.13	17.03	18.72
Females											
0.22 to <0.5	53	6.5 ± 0.9	3.26 ± 0.66	2.17	2.41	2.81	3.26	3.71	4.11	4.36	4.81
0.5 to <1	63	8.5 ± 1.0	3.96 ± 0.72	2.78	3.05	3.48	3.96	4.45	4.88	5.14	5.63
1 to <2	66	10.6 ± 1.3	4.78 ± 0.96	3.20	3.55	4.13	4.78	5.43	6.01	6.36	7.02
2 to <5	36	14.4 ± 3.0	7.06 ± 1.16	5.15	5.57	6.28	7.06	7.84	8.54	8.97	9.76
5 to <7	102	19.7 ± 2.3	8.22 ± 1.31	6.06	6.54	7.34	8.22	9.11	9.90	10.38	11.27
7 to <11	161	28.3 ± 4.4	9.84 ± 1.69	7.07	7.68	8.70	9.84	10.98	12.00	12.61	13.76
11 to <23	87	50.0 ± 8.9	13.28 ± 2.60	9.00	9.94	11.52	13.28	15.03	16.61	17.56	19.33
23 to <30	68	59.2 ± 6.6	13.67 ± 2.28	9.91	10.74	12.13	13.67	15.21	16.59	17.42	18.98
30 to <40	59	58.7 ± 5.9	13.68 ± 1.76	10.78	11.42	12.49	13.68	14.87	15.94	16.58	17.78
40 to <65	58	58.8 ± 5.1	12.31 ± 2.07	8.91	9.66	10.92	12.31	13.70	14.96	15.71	17.12
65 to ≤96	45	57.2 ± 7.3	9.80 ± 2.17	6.24	7.02	8.34	9.80	11.27	12.58	13.37	14.85

[a] Measured body weight. Normal-weight individuals defined according to the BMI cut-offs.

[b] Physiological daily inhalation rates were calculated using the following equation: $(TDEE + ECG) \times H \times (V_E/VO_2) \times 10^{-3}$, where $H = 0.21$ L of O_2/Kcal, $V_E/VO_2 = 27$ (Layton, 1993) and ECG = stored daily energy cost for growth (kcal/day).

- The default value for inhalation rate in workers is generally higher than that for the general population, based on consideration for potential higher activity levels. For example, Valdez-Flores et al. (2022) relied upon relative inhalation rates of 10 m^3/day (i.e., 1.25 m^3/hour for an 8-hour workday) and 20 m^3/day (i.e., 0.83 m^3/hour for a 24-hour day) for workers and general population, respectively, when adjusting between occupational and environmental exposures. Variation in the worker inhalation rates may be imputed based on those reported in **Table 2-9** based on consideration of the age and gender of the worker population considered.

2.2.3. Exposure Times (ET, hours/day) and Frequencies (EF, days/year)

- For adjusting between worker exposures and general population exposures, the following default assumptions for exposure times and frequencies will be used to maintain consistency with adjustments used in the derivation of toxicity values. To convert between environmental and occupational exposures, Valdez-Flores et al. (2022)

relied upon relative EFs of 240 and 365 days/year for workers and general population. For purposes of characterizing variation in these terms, ranges of 150-300 days/year and 300-365 days/year are proposed for workers and general population, respectively, based on professional judgement.

- Default assumptions for ET for workers and general population are 8 and 24 hours/day, respectively. For purposes of characterizing variation in these terms, a range of 6-12 hours/day is proposed for workers and a range of 16-24 hours/day is proposed for general population (further divided by times spent outdoors, indoors, and in vehicles as described below), respectively, based on professional judgement.
- For worker scenarios, workers will conservatively be assumed to be exposed to workplace air for the entire workday. For the general population exposures time spent indoors (i.e., exposed to indoor air).

Time Indoors (hours/day) = 24 hours/day – Time Outdoors – Time in Vehicles
Eq.5

- Distributions for the times spent outdoors and in vehicles are proposed to be defined by the data contained in **Tables 2-10** and **11**. Considerations for cumulative exposures across scenarios (e.g., worker plus general population) will be addressed in Round 5 of the review.

Table 2-10. Time Spent Indoors and Outdoors (USEPA EFH 2011; from Table ES-1)

	Time Indoors (total) minutes/day		Time Outdoors (total) minutes/day		Time In
	Mean	95th Percentile	Mean	95th Percentile	Mean
Birth to <1 month	1,440	-	0	-	-
1 to <3 months	1,432	-	8	-	-
3 to <6 months	1,414	-	26	-	-
6 to <12 months	1,301	-	139	-	-
Birth to <1 year	-	-	-	-	1,108
1 to <2 years	1,353	-	36	-	1,065
2 to <3 years	1,316	-	76	-	979
3 to <6 years	1,278	-	107	-	957
6 to <11 years	1,244	-	132	-	893
11 to <16 years	1,260	-	100	-	889
16 to <21 years	1,248	-	102	-	833
18 to <64 years	1,159	-	281	-	948
>64 years	1,142	-	298	-	1,175

Table 2-11. Time Spent in Vehicles (USEPA EFH 2011; from Table 16-24)

		Car											
								Percentiles					
Category	Population Group	*N*	Mean	SD	SE	Min	Max	5	25	50	75	90
All		6,560	87.4	88.2	1.1	1	1,280	10	34	63	110	175
Sex	Male	2,852	90.7	97.3	1.8	1	1,280	10	30	63	115	185
Sex	Female	3,706	84.9	80.4	1.3	1	878	10	35	64	110	165
Sex	Refused	2	30.0	14.1	10.0	20	40	20	20	30	40	40

2.2.4. Exposure Durations (ED, years)

- Central tendency values for ED in workers and general population are proposed to be based on the data provided in **Table 2-12**. For the purposes of characterizing variation in ED, ranges of 1-45 years and 1-78 years are proposed for worker and general population scenarios, respectively.

Table 2-12. Worker Tenure and Residence Times (USEPA EFH 2011; from Table ES-1)

	Median Tenure (years) Men		Median Tenure (years) Women	
All ages, ≥16 years	7.9		5.4	
16 to 24 years	2.0		1.9	
25 to 29 years	4.6		4.1	
30 to 34 years	7.6		6.0	
35 to 39 years	10.4		7.0	
40 to 44 years	13.8		8.0	
45 to 49 years	17.5		10.0	
50 to 54 years	20.0		10.8	
55 to 59 years	21.9		12.4	
60 to 64 years	23.9		14.5	
65 to 69 years	26.9		15.6	
≥70 years	30.5		18.8	
	Population Mobility			
	Residential Occupancy Period (years)		Current Residence Time (years)	
	Mean	95th Percentile	Mean	95th Percentile
All	12	33	13	46

- Definitions for lifetime duration will be based on U.S. life expectancies for men, women, and combined of 75 years, 80 years, and 78 years, respectively (USEPA EFH 2011).

2.2.5. Additional Exposure Items Considered in Round 5 of This Review

Please note that the following items will be addressed in the Round 5 of this review:

- Equations and Distributions for the calculation of occupation exposure limit values
- Values/distributions for protection factors (PF) values for different types of respirators.
- Assumptions to assess cumulative exposures across scenarios (i.e., what if someone lives near a BD facility, and is also a BD manufacture worker)
- Exposures to BD from tobacco smoke.
- Any additional topic areas based on panel input

2.3. Toxicity Parameter Values

- 1,3-Butadiene (BD) is a data-rich chemical, for which our understanding of its toxicity and carcinogenicity has greatly improved over the past 20 years.
- Assessments conducted by USEPA in 2002, as well as some other agencies, do not reflect the best available science (data and methods) for BD, and therefore should not be used to support human health risk assessments for this chemical under TSCA.
- Efforts have been made to update the cancer and noncancer assessments for BD using New Approach Methods (NAMs) that incorporate the best available data and scientific weight of evidence, and has resulted in multiple publications (**Table 2-13**). This table provides recommendations for the toxicity values, along with alternative toxicity values for BD that reflect different data sets, methods, and assumptions.
- An early draft of cancer dose-response assessments for BD were reviewed as a case study entitled "*Cancer Risk Assessment for 1,3-Butadiene: Incorporating New Data and Methods*" at the Alliance for Risk Assessment Beyond Science and Decisions Workshop XIII (ARA, 2022). Input received on the draft epidemiology- and rodent-based assessments was used to finalize the published versions of both assessments (Kirman and Hays., 2022; Valdez-Flores et al. 2022).

2-13. Summary of Proposed Toxicity Values for BD Based on Best Available Science

Toxicity Value Type (Tables)	Endpoint/Data Set	New Approach Methods (NAMs)	POD	Value	Supporting Values	Reference with Hyperlink
Cancer Unit Risk	Leukemia mortality in updated cohort of SBR workers (Sathiakumar et al. 2021)	Cox proportional hazards regression modeling for an aggregate mortality endpoint (leukemia + bladder cancer)	LEC000001 = 0.016 ppm	0.000086 ppm^{-1}	Worst-case unit risk based on aggregate leukemia + bladder cancer (causation assumed): 0.00013 ppm^{-1} Rodent-based unit risk range of values: 0.000014-0.00088 ppm^{-1}	Valdez-Flores et al. (2022)
Noncancer Reference Concentration, Short-term/ Subchronic	Fetal body weight changes in mice and rats (Hackett et al. 1987a,b)	Hemoglobin adduct data for BD metabolites were used to quantify species differences in internal dose to inform interspecies extrapolation	LEC0.5SD = 860 ppm	29 ppm	RfC based on mouse data alone: 57 ppm (UF total = 30) RfC based on rat data alone: 67 ppm (UF total = 30) Alternative uncertainty factors considered Alternative uncertainty factor values based on human variation data (e.g., Boysen et al. 2022) are also discussed	Kirman et al. (2022)
Noncancer Reference Concentration, Long-term/ Chronic	Ovarian atrophy in mice and rats (multiple studies, including the OECD 421 study in rats)	Hemoglobin adduct data for BD metabolites were used to quantify species differences in internal dose to inform interspecies extrapolation	LEC001 = 310 ppm	10 ppm	RfC based on mouse data alone: 47 ppm (UF total = 30) RfC based on rat data alone: 370 ppm (UF total = 30) Alternative uncertainty factors considered Alternative value for UFh based on	Kirman et al. (2022)

					new human variation information (Boysen et al. 2022) are also discussed	

To support a probabilistic risk assessment for BD, probability density functions can be defined for the POD values (i.e., via output from USEPA's BMDS software), values used to support interspecies scaling, and uncertainty factors (either based on data or plausible ranges based on policy or expert opinion provided by the panel). Input from the panel during Round 3 of this review will inform the distributions proposed for toxicity parameter values.

2.3.2. Available Agency Assessments for BD are Outdated

- USEPA's assessment for BD (USEPA, 2002) is more than twenty years old.
- USEPA, like most agencies and assessors, derived noncancer values based on fetal body weight changes and ovarian atrophy from studies in laboratory rodents, and derived cancer values based on leukemia in styrene-butadiene rubber (SBR) workers (**Table 2-14**).
    - At the time these assessments were prepared there were insufficient data to quantify species differences in the metabolic activation of BD, resulting in the use of conservative assumptions for interspecies extrapolation.
- Over the past two decades, two areas of research have greatly improved our understanding of BD's toxicity and carcinogenicity.
    - Based on robust data on metabolite-specific biomarkers (Swenberg et al. 2007, 2011; Georgieva et al. 2010; Boysen et al. 2012), we now have a much better understanding of the large species differences in metabolic activation that underly species differences in BD's potency. This research is not controversial. Because of these species differences ATSDR (2012, Section 2.3) decided to not adopt the conservative assumptions for BD, and therefore did not derive Minimal Risk Levels (MRLs) out of concern for overestimating potential risks to humans.
    - The SBR cohort has undergone multiple updates, and now includes more years of follow-up, refined exposure estimates, and data for female workers (see Table 1 from Valdez-Flores et al., 2022).

Table 2-14. Summary of Available Agency Assessments for BD

Assessor (Year)	Assessment	Endpoint	Data set	Toxicity Value	Note
Health Canada (2000)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	LEC05 = 0.44 mg/m^3	Interspecies extrapolation ap
	Cancer	Leukemia	SBR workers (Delzell et al. 1995)	TC01 = 1.7 mg/m^3	Cohort and exposures are no
USEPA (2002)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	RfCc = 0.9 ppb	Interspecies extrapolation ap
	Acute & Subchronic Noncancer	Fetal body weight	Mice (Hackett et al. 1987)	RfCs = 7 ppb	Interspecies extrapolation ap
	Cancer	Leukemia	SBR workers (Delzell et al. 1995)	0.08 (ppm-1)	Cohort and exposures are no
ATSDR (2012)	Acute, Intermediate, Chronic Minimal Risk Levels (MRLs)	ATSDR elected to not derive acute-, intermediate-, and chronic-duration inhalation minimal risk levels for I chemical-specific data to adjust for the large species differences in metabolism, which may result in the M risk to humans			
OEHHA (2013)	Acute Reference Exposure Level (REL)	Fetal body weight	Mice (Hackett et al., 1987; as reanalyzed by Green, 2003)	297 ppb	Interspecies extrapolation ap
	8-Hours REL	Ovarian atrophy	Female mice (NTP, 1993; Doerr et al., 1996)	4 ppb	Interspecies extrapolation ap
	Chronic REL	Ovarian atrophy	Female mice (NTP, 1993)	1 ppb	Interspecies extrapolation ap
	Inhalation unit risk (NSRL basis)	Multiple tumors	Mice (NTP, 1984; Melnick et al. 1990)	0.00017 (ug/m3)-1	Interspecies extrapolation ap
TCEQ (2015)	Chronic Noncancer	Ovarian atrophy	Female mice (NTP, 1993)	15 ppb	Interspecies extrapolation ap
	Acute Noncancer	Fetal body weight	Mice (Hackett et al. 1987)	430 ppb (24-hr)	Interspecies extrapolation ap
	Chronic cancer inhalation unit risk	Leukemia	SBR workers (Sathiakumar and Delzell, 2009)	5.0E-07 per µg/m3 (1.1E-06 per ppb)	Cohort is not current

- Because the assessments listed in **Table 3-2** do not reflect the scientific weight of evidence, they are not recommended for use in human health risk assessment of BD exposures under TSCA.

2.3.3. Updated Assessments Have Been Conducted and Published for BD

2.3.3.1 Unit Risk Values for BD Based on Updated SBR Cohort Data (Male and female SBR workers followed through 2009; Sathiakumar et al., 2021a,b)

- The cohort of SBR workers has undergone multiple updates over the past 20 years:
  - Delzell (1995) – Original cohort of male workers followed through 1991, relied upon by USEPA in 2002 assessment

- Sathiakumar et al. (2005) – 1st update of male workers followed through 1998 with refined exposure estimates
- Sathiakumar and Delzell (2009) – Assessment of female workers followed through 2002
- Sathiakumar et al. 2019 – Update of male and female workers combined, followed through 2009

- The latest SBR cohort data (Sathiakumar et al. 2021a,b) has been used to estimate unit risk values for BD using Cox proportional hazards regression to account for significant exposure and non-exposure covariates (Valdez-Flores et al. 2022; **Table 3-3**).
  - Unit risk values based on leukemia mortality in male and female workers that include statistically significant covariates (BD High Intensity Tasks or HITs; row 1 of **Table 3-3**) are considered to represent the best available science for BD (high quality cohort with long follow-up, excellent exposure data, careful consideration of exposure and nonexposure covariates).
  - Alternative unit risk values have been derived using a NAM (e.g., aggregate of leukemia and bladder cancer mortality data within Cox proportional hazards regression), with and without consideration of covariates, are also provided to provide flexibility to risk assessors and risk managers.
  - This assessment has undergone additional peer review as part of an Alliance for Risk Assessment workshop (ARA, 2022). Comments received during this review were used to finalize the assessment for publication (Valdez-Flores et al. 2022).

Table 2-15. Summary of Epidemiology-Based Unit Risk Values (Valdez-Flores et al. 2022)

Endpoints	Cox Proportional Hazards Regression Covariates	POD EC000001 (LEC-UEC), ppm	Unit Risk (ppm-1)
Leukemia	BD HITs	0.0271 (0.0116 – NA)	0.000037 (NA -0.000086*)
NAM: Aggregate (Leukemia and bladder cancer mortality)	BD HITs and Sex	0.0129 (0.0076 – 0.0418)	0.000078 (0.000024 – 0.0001
Leukemia	None	0.0127 (0.0085 – 0.025)	0.000079 (0.000040 – 0.0001
NAM: Aggregate (Leukemia and bladder cancer mortality)	None	0.0075 (0.0056 – 0.011)	0.00013 (0.000091 – 0.00018

*Value recommended for the 95% UCL for cancer potency

2.3.3.2 Updated Unit Risk Values for BD Based on Rodent Data

- Metabolism of BD is an important determinant of its toxicity and carcinogenicity, with emphasis placed on the formation of 3 reactive epoxide metabolites:
  - EB = 2,3-epoxy-1-butene
  - DEB - 1,2,3,4-diepoxybutane
  - EBD = 3,4-epoxybutane-1,2-diol
- Although existing physiologically-based pharmacokinetic (PBPK) models for BD do not account for key differences in metabolic activation of BD to support interspecies extrapolation, biomarker data (i.e., metabolite-specific hemoglobin adducts) are available in mice, rats, and humans to support this extrapolation.
- Based on these data, metabolic activation of BD in humans, particularly the formation of the potent diepoxide metabolite (DEB), is much lower than assumed in previous assessments for BD.
- A NAM was used in the unit risk derivation based on rodent data that relies on metabolite-specific biomarkers to quantify species differences in the internal dose of BD metabolites has been developed (Fred et al. 2008; Motwani and Tornqvist, 2014).
- The approach of Fred et al. (2008) and Motwani and Tornqvist (2014) has been extended and applied to the derivation of unit risk values for BD (Kirman and Hays, 2022) extrapolated from rodent data, which considers species differences in the formation of reactive metabolites, as well as differences in the genotoxic potencies for these metabolites (DEB>>EBD~EB; **Table 3-4**).

Table 2-16. Summary of Genotoxic Potencies for BD Metabolites (from Kirman and Hays, 2022)

	Metabolite[1]				
Endpoint	**EB**	**DEB**	**EBD**	***In Vitro* Cell System**	**Reference**
DNA Damage	1.00	11.21	0.961	Human hepatocytes, pH 11.9	Wen et al. 2011; Zhang et al. 2012
	1.00	4.22	0.955	Human hepatocytes, pH 9	
DNA Damage Mean±SD	*1.00*	*7.72±4.94*	*0.96±0.004*		
Mutations	1.00	81.66	2.10	Human TK6 (HPRT)	Meng et al. 2010
	1.00	277.12	4.46	Human TK6 (TK)	
	1.00	58.10	0.45	Human TK6 (HPRT)	Cochrane and Skopec (1994)
	1.00	114.83	0.71	Human TK6 (TK)	
	1.00	49.08	0.35	BB Mouse Fibroblasts	Erexson and Tindall (2000)
	--[2]	--[2]	--[2]	BB Rat Fibroblasts	
	1.00	4.20	3.87	SA T100	Adler et al. (1997)
Mutations Mean±SD	*1.00*	*97.5±95.3*	*1.99±1.81*		
Micronuclei	1.00	128.28	0.58	BB Mouse Fibroblasts	Erexson and Tindall (2000)
	1.00	124.08	0.74	BB Rat Fibroblasts	
	--[2]	--[2]	--[2]	Rat spermatids	Sjoblom and Kahdetie, 1996
Micronuclei Mean±SD	*1.00*	*126.18±2.97*	*0.66±0.12*		
Overall Mean±SD[3]	***1.00***	***85.28±82.81***	***1.52±1.48***		

[1]Relative potencies calculated based on the ratio of linear slopes for each metabolite relative to the slope for EB assessed in the same cell test system.
[2]Only DEB yielded a positive response, therefore relative potencies were not estimated for this data set.
[3]Values used to support calculation of data-derived extrapolation factors.

- Unit risk values for BD based on rodent data using this approach are provided in **Table 3-5**. Values are provided for each species and sex, as well as providing different confidence limit values (MLE, 95% LCL, 95% UCL), to provide flexibility to risk assessors and risk managers.
- The use of hemoglobin biomarkers to support interspecies extrapolation for BD is consistent with USEPA's approach for using biomarker data to derive cancer potency estimates for acrylamide (IRIS, 2010).

Table 2-17. Summary of Rodent-Based Unit Risk Values for BD (Kirman and Hays, 2022)

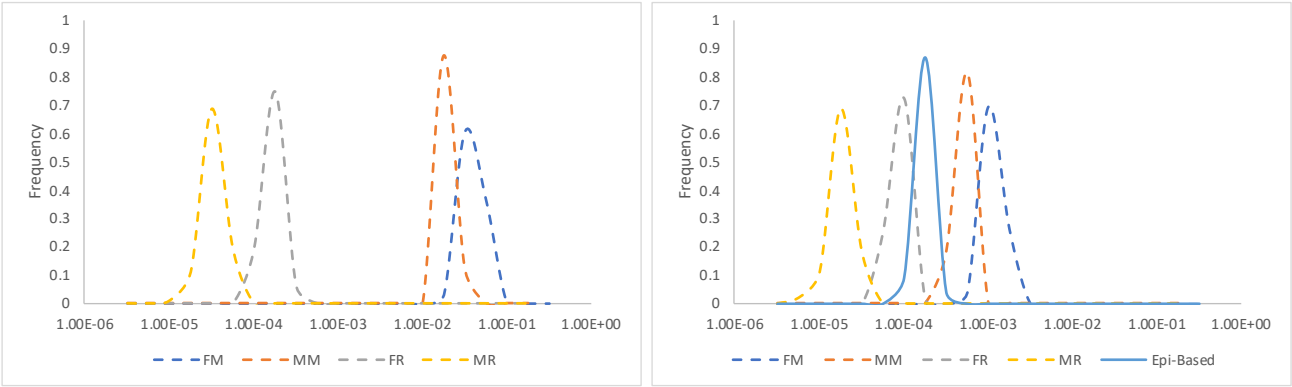
Data Set			Range of Model Fit Statistics for Individual Tumor Types		Unit Risk for Combined Tumor Types (ppm^{-1} HEC)*
Data Set	N	Range of Observation, (HEC, ppm continuous)	p-Values	AICs	
Female Mouse	558	52-27800	0.103-0.867	81.6-349.1	8.8E-04 (5.7E-04 – 1.2E-03)
Male Mouse	756	49-36550	0.052-0.966	35.6-337.3	3.5E-04 (2.8E-04 – 4.3E-04)
Female Rat	300	336-2690	0.00016-0.969	35.7-357	6.7E-05 (4.2E-05 – 9.6E-05)
Male Rat	300	321-2570	0.131-0.163	88.7-109	1.4E-05 (7.5E-06 – 2.1E-05)

*HEC = Interspecies adjustments made assuming all 3 genotoxic epoxide metabolites contribute to the observed tumorigenic response in rodents

- Rodent-based unit risk values are considered supportive of the epidemiology-based unit risk values summarized above (**Table 3-3**).
- Accounting for species differences in the metabolic activation of BD results in improved concordance of potency estimates for BD (**Figure 2-1**).
- This assessment has undergone additional peer review as part of an Alliance for Risk Assessment workshop (ARA, 2022). Comments received during this review were used to finalize the assessment for publication (Kirman and Hays, 2022).

Figure 2-1. Concordance of unit risk distributions (Kirman and Hays, 2022): (A) unadjusted exposure and (B) adjusted for species differences in internal dose and genotoxic potency of BD metabolites; unit risk values based on epidemiology data are from Valdez-Flores et al. (2022).

(A) (B)



2.3.3.3 Updated Reference Concentrations for BD Based on Rodent Data

- A NAM was used in the derivation of reference concentrations based on rodent data. Specifically, the approach of Fred et al. (2008) and Motwani and Tornqvist (2014) was also extended and applied to the derivation of reference concentration values for BD (Kirman et al. 2022), which considers species differences in the formation of reactive metabolites, as well as differences in the cytotoxic potencies for these metabolites (DEB>>EBD~EB; **Table 2-18**). This approach is the same as that described above for deriving a unit risk value for BD based on rodent data, but relies on metabolite-specific cytotoxic potencies rather than genotoxic potencies.

Table 2-18. Summary of Cytotoxic Potencies (Kirman et al. 2022)

	Metabolite[1]			
Reference	**EB**	**DEB**	**EBD**	***In Vitro* Cell System**
Irons et al. (2000)	1.00	58.6	1.04	Human CD34+ bone marrow cells
Meng et al. (2010)	1.00	79.9	0.681	Human TK6 cells
Cochrane and Skopec (1993)	1.00	112	0.553	Human TK6 cells
Erexson and Tindall (2000)	1.00	74.1	0.556	BB mouse fibroblasts
Erexson and Tindall (2000)	1.00	32.9	0.000	BB rat fibroblasts
Nakamura et al. (2021)	1.00	670	0.63	Chicken B lymphoid cells
Arithmetic Mean±SD[2]	*1.00±0.00*	*171±246*	*0.578±0.334*	

[1]Relative potencies calculated based on the ratio of linear slopes for each metabolite relative to the slope for EB assessed in the same cell test system.

[2]Arithmetic mean values were used to quantify relative cytotoxic potencies in mice, rats, and humans.

- Subchronic and chronic reference concentration values for BD based on rodent data using this approach for the same noncancer endpoints selected by regulatory agencies in the past (**Table 2-14**) are provided in **Table 2-19**. Reference concentration values are provided for different endpoints (i.e., fetal body weight changes, ovarian atrophy), species (i.e., mouse, rat, both species combined), and uncertainty factor values (i.e., 10, 30, 100), to provide some flexibility to risk assessors and risk managers.

- The rat data set used to derive the chronic RfC values based on ovarian atrophy includes a recently published OECD 421 guideline study conducted in rats (Marty et al. 2021).

Table 2-19. Summary of Rodent-Based Reference Concentrations (Kirman et al. 2022)

Parameter	Subchronic RfCs Based on Fetal Body Weight Changes			Chronic RfCs Based on Ovarian Atrophy		
Data Set	Combined	Mouse	Rat	Combined	Mouse	Rat
POD_{HEC} (ppm continuous)	BMDL0.5SD = 860	BMDL1SD = 1,700	NOAEL = 2,000	BMDL01 = 310	BMDL10 = 1,400	NOAEL = 11,000
Inter species Variation (UFa)	1-3					
Intraspecies Variation (UFh)	3-10					
LOAEL-to-NOAEL Extrapolation(UFl)	1					
Subchronic-to-Chronic Extrapolation (UFs)	1					
Database Uncertainty (UFd)	1-3					
Total Uncertainty Factor (UFT) (plausible range)	30 (10-100)					
RfC (ppm continuous)	29[2] (8.6-86)	57 (17-170)	67 (20-200)	10[3] (3.1-31)	47 (14-140)	370 (110-1,100)
RfC (ppm occupational)[4]	84 (25-250)	160 (50-500)	190 (58-580)	30 (9.1-91)	140 (41-410)	1,100 (320-3,200)

[1]Best UFT value (range of plausible values indicated in parentheses).
[2]Selected as the subchronic RfC for BD.
[3]Selected as the chronic RfC for BD.
[4]Calculated from continuous RfC assuming exposure frequencies of (250 vs 365 days/year) and breathing rates (10 m^3/day vs. 20 m^3/day).

- Although a plausible range of default uncertainty factor values are included in **Table 2-19**, there are recently published biomarker data that can be considered for quantifying human variation:
    - The hemoglobin biomarker data of Boysen et al. (2022) are considered to be the most useful for the purposes of quantifying human variation.
        - These are the same human biomarker data used in Motwani and Tornqvist (2014), Kirman and Hays (2022), and Kirman et al. (2022) to quantify species differences in metabolic activation of BD.
        - Note that some of the observed variation in Hb adducts may be attributable to variation in BD air concentrations to which workers are exposed (ideally assessors should adjust for this contribution).
        - For the subchronic RfC based on fetal BW changes, variation in EBD adducts, the primary contributor (~94%) to human cytotoxicity index (Kirman et al. 2022), is generally consistent with the default UF-TK of 3 used in Kirman et al. (2022).

        - However, for the chronic RfC based on ovarian effects attributed to DEB, variation in DEB at the upper tail as characterized by Boysen et al. (2022) is slightly larger than the default value of 3 (e.g., values of 4.3 and 7.9 and the 95% and 99% confidence level, respectively) , and should be considered as the basis for a data-derived uncertainty factor. These data would support a slightly lower chronic RfC value than derived in **Table 2-19**.
    - Urinary biomarker data (e.g., Erber et al. 2021) are considered less useful for characterization of human variation for subchronic and chronic risk assessment since: 1) Urinary biomarkers are generally more variable than hemoglobin adducts, and are more sensitive to temporal factors (intraday variation, time between exposure and urine collection; ideally assessors should adjust for these factors); 2) some of the observed variation in Hb adducts may be attributable to variation in BD air concentrations to which workers are exposed (ideally would want to adjust for this contribution); 3) biomarkers for the metabolite EB are not particularly useful since other metabolites (EBD & DEB) are considered to be primary contributors to toxicity and carcinogenicity of BD in humans (Kirman and Hays, 2022; Kirman et al. 2022).

2.3.3.4. Toxicity Values for Acute Risk Assessment

- Although an acute reference concentration was not specifically derived here for assessing single day or hourly exposures to BD, possible options for an acute value include the following:
    - USEPA's Acute Exposure Guideline Levels (AEGLs; NAS, 2009), which describe the human health effects to the general public from rare exposure to airborne chemicals (e.g., chemical spills), could be considered. AEGL values derived by USEPA for BD include those for three levels of effect severity:
        - AEGL1 = 670 ppm, based on difficulty focusing in humans
        - AEGL2 = 2700 ppm, based on no effects in humans
        - AEGL3 = 6800 ppm, based on lethality in rats

      AEGL values are applicable to acute BD exposure times ranging from 10 minutes to 8 hours.
    - The subchronic reference could be used as a health-protective surrogate to assess acute exposures to BD. This practice is consistent with the use of fetal body weight effects to derive acute RfVs for BD by other agencies (**Table 2-14**), and it is considered health protective due to differences in exposure duration (e.g., a single day exposure that reflects a small fraction of the human gestation period vs. a 10-day exposure from Hackett et al. (1987a,b) that reflects a large fraction of the rodent gestation period). RIVM (2003) recommended that the relevance of fetal body weight changes for acute limit setting be evaluated within the context of developmental effects and maternal toxicity. Furthermore, RIVM assessed the relative potency of single day vs repeated exposures to a variety of chemicals and reported that the NOAEL values for single-day exposures were on

average 3.5-fold higher than the NOAEL values for repeat exposures, and the LOAEL values for single-day exposures were on average 4.8-fold higher than the LOAEL values for repeat exposures. For this reason, additional adjustments may be needed before subchronic reference concentration values could be applied to assess single-day and/or hourly exposures to BD in air.

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3. Review Material for Round 5

3.1. Introduction

The text below briefly describes the methods, data, and assumptions for several aspects of the risk assessment for 1,3-butadiene (BD):

- Continuation of Round 3 and 4 discussions on Cox proportional hazards (CPH) modeling
- Derivation of occupational exposure values
- Use of biomarker data (hemoglobin adducts) to characterize human variation in the internal dose of BD metabolites
- Protection factor assumptions for different worker respirator categories
- Aggregation of exposures across scenarios
- Estimation of hazards and risks from BD due to exposures from smoking

3.2. CPH Modeling

3.2.1 Assumptions Violation

Because the regression model includes time-dependent variables (e.g., cumulative BD ppm-years) the assumption of proportional hazards model does not apply but the partial likelihood approach developed for the model can still be applied. Since the hazard ratios do not remain constant, it is not a proportional hazards model in the classical sense. However, the partial likelihood method associated with the CPH model can still be used to estimate model parameters. As stated by Paul Allison, "*If the assumption is violated for a particular predictor variable, it simply means that the coefficient for this variable represents a kind of "average" effect over the period of observation. For many applications, this may be sufficient*." (https://statisticalhorizons.com/wp-content/uploads/2012/01/Allison_SurvivalAnalysis.pdf). This serves as a key assumption in the assessment, that the CPH model as applied here provides results that are sufficient for risk assessment purposes.

For the BD risk assessment, we recommend proceeding with this approach and make this assumption explicit. This approach is consistent with the paradigm that agencies such as USEPA (in their recent assessments for ethylene oxide and formaldehyde) and TCEQ (in their recent assessments for BD and ethylene oxide), and therefore this particular issue extends well beyond the BD assessment. We also recommend including discussion of methods for improving exposure-response assessment using epidemiology data for risk assessment for regulatory agencies (highlighting the need for guidelines on this topic).

3.2.2 Consideration of Covariates

In Rounds 3 and 4 there has been some discussion regarding the identification of covariates to include in the Cox proportional hazards (CPH) regression model (e.g., recommendations to include direct acyclic graphs or DAGs to inform covariate selection; DAGs are a technique that can be used to define relationships and dependencies of factors or variables leading to a specific result, to inform covariate selection).

The covariate decisions made in Valdez-Flores et al. (2022) were not made in isolation. Over the years the SBR cohort data has been extensively modeled using the Cox proportional hazard regression by two independent groups (University of Alabama researchers; and independent consultants, Drs. Sielken and Valdez-Flores), these analyses have included many combinations of non-exposure covariates, as summarized in **Table 3-1**.

Table 3-1. Historical Perspective on Covariates Used in CPH Modeling for the SBR Cohort

Reference	Non-Exposure Covariate	Slope term for cumulative BD ppm-years in CPH model
Cheng et al. 2007	Age	0.00029
Sielken et al. 2007	Age	0.00029
Sielken and Valdez-Flores 2011	Age	0.00029
Sathiakumar et al. 2015	Age	0.00026
Sielken et al. 2015	Age	0.00029
Valdez-Flores et al. 2022	Age	0.00028
Sielken et al. 2007	Age, HITS	0.00022
Sielken and Valdez-Flores 2011	Age, HITS	0.0002
Sielken et al. 2015	Age, HITS	0.0002
Valdez-Flores et al. 2022	Age, HITS	0.00013
Sielken et al. 2007	Age, Years since hire	0.00029
Sielken and Valdez-Flores 2011	Age, Years since hire	0.00029
Sielken et al. 2007	Age, Race	0.00026
Sielken and Valdez-Flores 2011	Age, Race	0.00026
Sielken et al. 2007	Age, Plant	0.00039
Sielken and Valdez-Flores 2011	Age, Plant	0.00039
Sielken et al. 2007	Age, Calendar year	0.00029
Sielken and Valdez-Flores 2011	Age, Calendar year	0.00028
Sathiakumar et al. 2015	Age, Race, plant	0.00029
Sathiakumar et al. 2021a	Age, Race, plant, sex, age at hire, year of hire, ever hourly status	0.00026
Valdez-Flores et al. 2022	None	0.00029

These results demonstrate that the slope of the CPH regression modeling has remained relatively stable with multiple updates to the SBR cohort (note- the slope term from the CPH regression is not the same as the inhalation unit risk. This value is used within lifetable calculations to derive the inhalation unit risk). With the exception of high intensity tasks (HITS), the slope of the CPH regression not meaningfully affected (at least for risk assessment purposes) by the inclusion/exclusion of the different covariates.

Sathiakumar et al. (2021a) considered many reduced versions of the model (i.e., those that include only a subset of covariates) as part of their sensitivity analysis. The goal of the reduced models was to preserve the control of confounding, while providing more precise results. The

authors concluded that the "*use of the reduced models did not identify any additional statistically significant results*".

Valdez-Flores et al. (2022) builds upon the results in Sathiakumar et al. (2019, 2021a) and previously to develop an exposure response model that best described the relationship for six cancer endpoints identified as significantly increased with exposure to butadiene. Sathiakumar et al. 2019 and 2021 summarizes the following significant findings:

1. All leukemia: "Using untrimmed butadiene ppm-years, the exposure–response trend was statistically significant."
2. Lymphoid leukemia: "exposure–response trends were statistically significant."
3. Myeloid leukemia: "the RR for each butadiene exposure quartile was elevated but statistically imprecise, and none of the exposure–response trends was significant."
4. Multiple myeloma: "No statistically significant butadiene exposure–response was found for multiple myeloma." "Matanoski et al. (1997) reported that multiple myeloma was associated with butadiene in a study that included most of the subjects in our male cohort, in contrast to our analyses by cumulative exposure, which provided no support for an association with butadiene or styrene."
5. Non-Hodgkin's lymphoma (NHL): "no exposure–response was detected in analyses of exposure quartile or trends using untrimmed butadiene ppm-years. However, trimming to restrict data to ppm-years >0and ≤95th percentile (1083 ppm-years) yielded a trend p value of 0.002."
6. Bladder/urinary cancer: "Increased bladder cancer mortality was seen among both men and women in the overall cohort. An excess of this cancer was particularly evident in hourly employees with 30 or more years since hire and 10 or more years of employment, and internal analyses further indicated a positive association with monomer exposure, with a statistically significant exposure– response trend."

While the desire for statistical rigor (e.g., incorporation of DAG) is certainly appreciated, it seems unlikely that such efforts would yield meaningful changes to the CPH modeling and subsequent risk assessment for BD. For this reason, we recommend proceeding with existing CPH modeling results from Valdez-Flores et al. (2022) with the inclusion of some discussion of potential future refinements that can include the implementation of DAG.

3.3. Occupational Exposure Values

- Occupational exposure values (OEV) for BD will be calculated using formulas modeled after those used by USEPA for formaldehyde (USEPA, 2024). These equations are essentially a rearrangement of the equations used to calculate hazard and risk described in the Round 3 Summary Report.

    - For noncancer endpoints:

$$OEV_{nc} = (POD_{HEC} / MOE) \times (AT_{nc} /(ET \times EF)) \times (BR) \qquad Eq.1$$

- For cancer endpoints:

$$OEV_c = (TR / IUR) \times (AT_c / (ET \times EF \times ED) \times (BR) \quad Eq.2$$

Where,

- ATnc = Averaging time for noncancer endpoints (hours)
- ATc = Averaging time for the cancer endpoints (hours)
- MOE = Acceptable margin of exposure (or total uncertainty factor)
- TR = Target risk for excess lifetime cancer risk
- OEVnc = Occupational exposure limit based on noncancer endpoints
- OEVc = Occupational exposure limit based on cancer endpoints
- ET = Exposure time (hours/day)
- EF = Exposure frequency (days/year)
- ED = Exposure duration (year)
- POD_{HEC} = Human equivalent concentration for the noncancer point of departure
- IUR = Inhalation unit risk (risk per ppm)
- BR = Breathing rate ratio (unitless), if needed, this value will be calculated as default inhalation rate for the general population divided by inhalation rate for the worker population.

- The parameter values used in these equations will rely upon the same data sets provided in the Round 3 Summary Report to support the risk assessment, modified as needed by panel recommendations. Additionally, a decision will need to be made regarding an appropriate MOE (i.e., uncertainty factors) for occupational exposures, since a smaller MOE value is sometimes used for worker populations compared to the value used for the general population (note- this will serve as the basis of a charge question in Round 5).

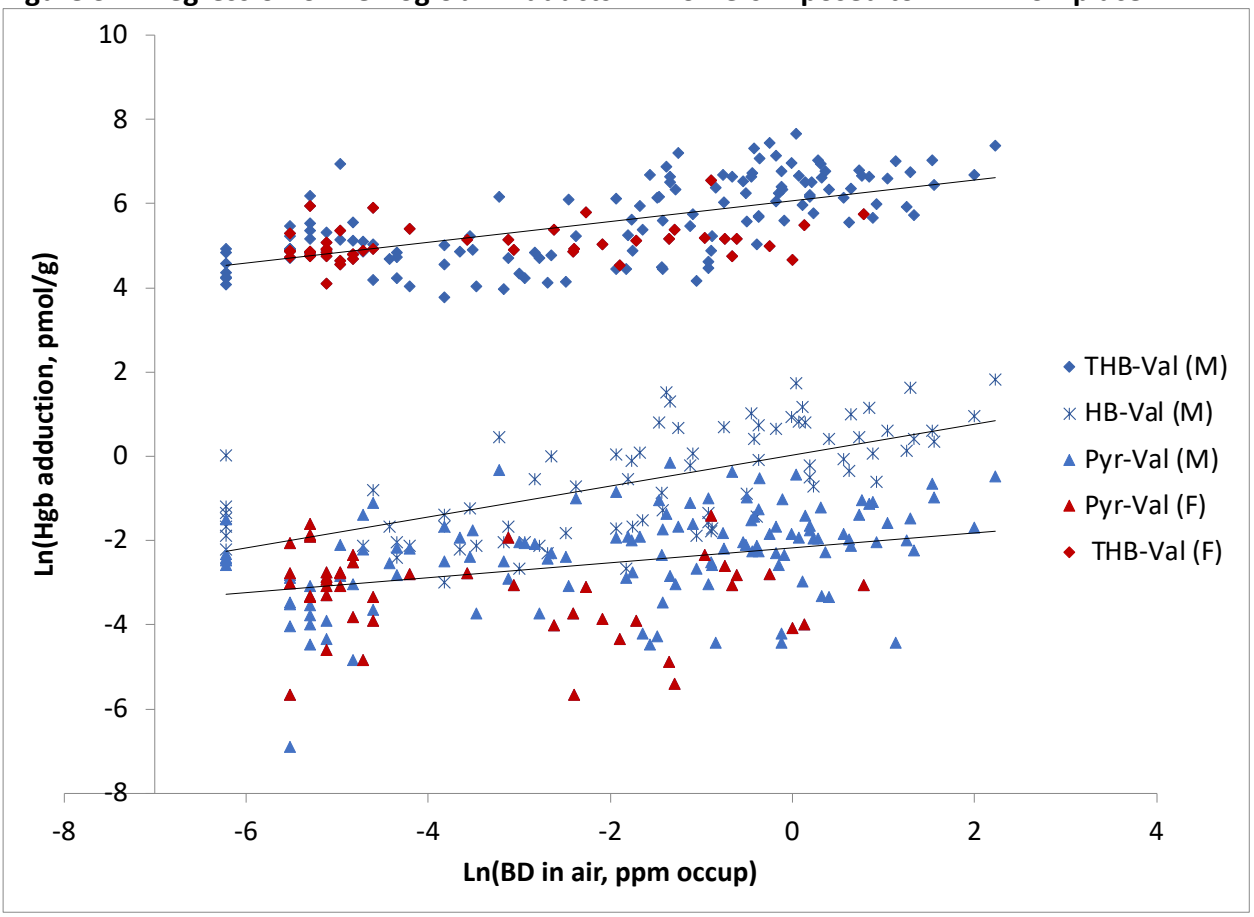
3.4. Use of Hemoglobin Adduct Data to Characterize Human Variation

- Biomarker data (hemoglobin adducts) are available to characterize variation in the internal dose of the three BD epoxide metabolites: (1) HB-val, which reflects the internal dose of the mono-epoxide metabolite, (2,3-epoxy-1-butene or EB); (2) pyr-val, which reflects the internal dose of the di-epoxide metabolite (1,2,3,4-diepoxybutane or DEB); and (3) THB-val, which reflects the internal dose of mono-epoxide diol metabolite (3,4-epoxybutane1,2-diol or EBD).
- As described in the Round 3 Summary Report, Boysen et al. (2022) characterized variation in pyr-val adducts at the upper tail of the distribution which is slightly larger (e.g., values of 4.3 and 7.9 at the 95% and 99% confidence level, respectively) than the default value of 3 for human toxicokinetic variation (i.e., the default uncertainty factor of 10 for human variation is comprised of factors of ~3.2 each to toxicokinetic and

toxicodynamic factors). The data assessed in Boysen et al. (2022) reflect samples collected as part of the first study in male Czech workers (Albertini et al. 2003).

- A second study was also conducted in Czech workers (Vacek et al. 2010), which included blood samples collected from male and female workers. At the time the study was published, analytical methods were sufficiently sensitive to detect THB-val adducts, but were not sensitive to detect pyr-val adducts in these workers. Since that time, analytical methods were improved for pyr-val adducts (Boysen et al. 2012) and the samples reanalyzed, but the results have not been published. With the permissions of Drs. Gunnar Boysen and Richard Albertini, we have been granted access to the published and unpublished individual data from both studies.
- Data and regression analyses have been conducted for the data from both studies (**Figure 3-1**). Within this figure different symbols are used for each adduct type, blue symbols depict male worker data, red symbols depict female worker data. Solid lines depict regressions for both sexes combined (additional regressions for females alone are not shown).

Figure 3-1. Regression of Hemoglobin Adducts in Workers Exposed to BD in Workplace Air



- Adduct burdens for THB-val and pyr-val in females (red markers) appears to be lower than males (blue markers) for a given BD exposure (**Figure 3-1**). Data for the HB-val adduct, which reflects internal doses of EB, are not available for study 2.
- The residuals (distance between data points and regression lines) can be used to quantify human variation, as summarized in **Table 3-2** for different data sets, biomarkers, and combined adducts using a cytotoxicity index (as calculated in Kirman et al. 2022).

Table 3-2. Characterization of Human Variation Using Hemoglobin Adduct Data for BD Metabolites in Exposed Workers

		Residual Percentile				
Worker Gender (Study)	**Adduct**	**1st**	**5th**	**50th**	**95th**	**99th**
Males (Study 1; as reported in Boysen et al. 2022)	pyr-val (reflects DEB internal dose)	NR	NR	NR	4.3	7.9
Males and Females (Studies 1 & 2)		0.049	0.13	1.2	5.0	7.5
Females (Study 2)		0.086	0.15	1.2	3.8	6.1
Males (Study 1)	Combined[1]	0.28	0.39	1.0	3.4	4.5
Females (Study 2)	Combined[1,2]	0.45	0.55	0.9	2.2	3.2
Males and Females (Studies 1 & 2)	Combined[1,2]	0.25	0.34	1.0	2.9	4.2

[1]For combined adducts, the cytotoxicity index approach was used as described in Kirman et al. (2022) and calculated for each individual worker to account for different toxic potencies of the three BD epoxide metabolites
[2]Because HB-val adduct data are not available for female workers, the combined percentiles do not include contributions from HB-val in females. However, the contribution of the monoepoxide metabolite was found to be a negligible contributor in male workers (~0.4% of cytotoxic index) so it may not reflect a meaningful data gap.
NR=not reported
Shaded cells defined in text below

- For application to human health risk assessment, we proposed the following:
    - The default uncertainty factor of 10 for intra-human variation can be considered to be comprised of equal components (half-log values of ~3.2 each) for toxicokinetic variation and toxicodynamic variation.
    - The default value of 3.2 for toxicokinetic variation should be replaced by an upper percentile value (e.g., 95th or 99th) of the residuals for regressions based on hemoglobin adducts. For the ovarian atrophy endpoint attributed to DEB, one of the values hi-lighted in green (**Table 3-2** above) could be adopted. Similarly, for the fetal body weight change endpoint attributed to all three epoxide metabolites, one of the values hi-lighted in yellow (**Table 3-2** above)could be adopted.
    - Refined uncertainty factor values for intra-human variation are calculated as the product of the selected values (for toxicokinetic variation) and 3.2 (for toxicodynamic variation). For example, if the 99th percentile value based on adducts in female workers from Study 2 are selected for both endpoints, then uncertainty factor values are calculated as ~20 (6.1x3.2) and ~10 (3.2x3.2) for ovarian atrophy and fetal body weight changes, respectively.

3-5. Worker Protection Factors for Respirator Use

- OSHA requires the use of respirators to protect health of employees from harmful dusts, fogs, fumes, mists, gases, smokes, sprays, or vapors (Respiratory Protection Standard 1910.134). When used properly, respirators reduce worker exposures to BD.

- Three categories of respirator used by BD manufacture workers are documented in Panko et al. (2023) (**Table 3-3**), and their use is presumed by other workers who are exposed to BD. The supplied air respirators in this table include full facepiece supplied air and full facepiece self-contained breathing apparatus (personal communication with Ms. Panko). The selection of an appropriate respirator depends on several factors, in addition to the concentration of the substance in air. NIOSH and OSHA have developed guidance for the selection of respiratory protection. To select the type of respirator for the activity in question, it is important to use not only the APF, but also estimate the Maximum Use Concentration (MUC), and duration of the activity, and other factors.

Table 3-3. Respirator Use by BD Manufacture Workers (Panko et al. 2023)

	1,3-BD Workplace air concentration ranges (ppm) reported with respirator use			
Task	Supplied Air	Full-Face APR	Half-Face APR	No Respirator
Unloading & Loading	<0.118–89	<0.06–36	<0.05–2.2	–
Handling Waste	–	<0.25–<3.7	<0.08–<0.1	–
Cleaning & Maintaining Equipment	<0.15–120	<0.02–110	<0.04–<0.7	<0.4–<0.7
Sampling Collection & Analysis	<0.52	<0.06–12	<0.09–7.3	<0.02–4.8
Performing Other Tasks	0.27–4.7	<0.24–<0.42	<0.2–<0.3	<0.39–<0.67

Note: APR = air-purifying respirator.

- OSHA has determined assigned protection factor (APF) values for various respiratory categories (**Table 4**). APFs defined by OSHA in this table are intended to be protective of workers (i.e., precautionary), and reflect the 5th percentile for the distribution of worker protection factors (WPFs). A WPF is based on a study, conducted under actual conditions of use in the workplace, that measures the protection provided by a properly selected, fit tested, and functioning respirator, when the respirator is worn correctly and used as part of a comprehensive respirator program that is in compliance with OSHA's Respiratory Protection standard. In the absence of sufficient WPF data, APFs are established by expert consensus using simulated workplace protection factors or other information. The APF takes into account all potential sources of facepiece penetration (e.g., face seal penetration, filter penetration, valve leakage). It does not account for factors that degrade protection such as poor maintenance, failure to follow manufacturer's instructions, and failure to wear the respirator during the entire exposure period (Janssen and McKay, 2017).

Table 3-4. Assigned Protection Factors (APFs) for Respirators (OSHA, 2009)

Type of Respirator[1, 2]	Quarter mask	Half mask	Full facepiece	Helmet/Hood	Loose-fitting facepiece
1. Air-Purifying Respirator	5	10[3]	50	—	—
2. Powered Air-Purifying Respirator (PAPR)	—	50	1,000	25/1,000[4]	25
3. Supplied-Air Respirator (SAR) or Airline Respirator					
• Demand mode	—	10	50	—	—
• Continuous flow mode	—	50	1,000	25/1,000[4]	25
• Pressure-demand or other positive-pressure mode	—	50	1,000	—	—
4. Self-Contained Breathing Apparatus (SCBA)					
• Demand mode	—	10	50	50	—
• Pressure-demand or other positive-pressure mode (e.g., open/closed circuit)	—	—	10,000	10,000	—

Notes:

[1] Employers may select respirators assigned for use in higher workplace concentrations of a hazardous substance for use at lower concentrations of that substance, or when required respirator use is independent of concentration.

[2] The assigned protection factors in Table I are only effective when the employer implements a continuing, effective respirator program as required by this section (29 CFR 1910.134), including training, fit testing, maintenance, and use requirements.

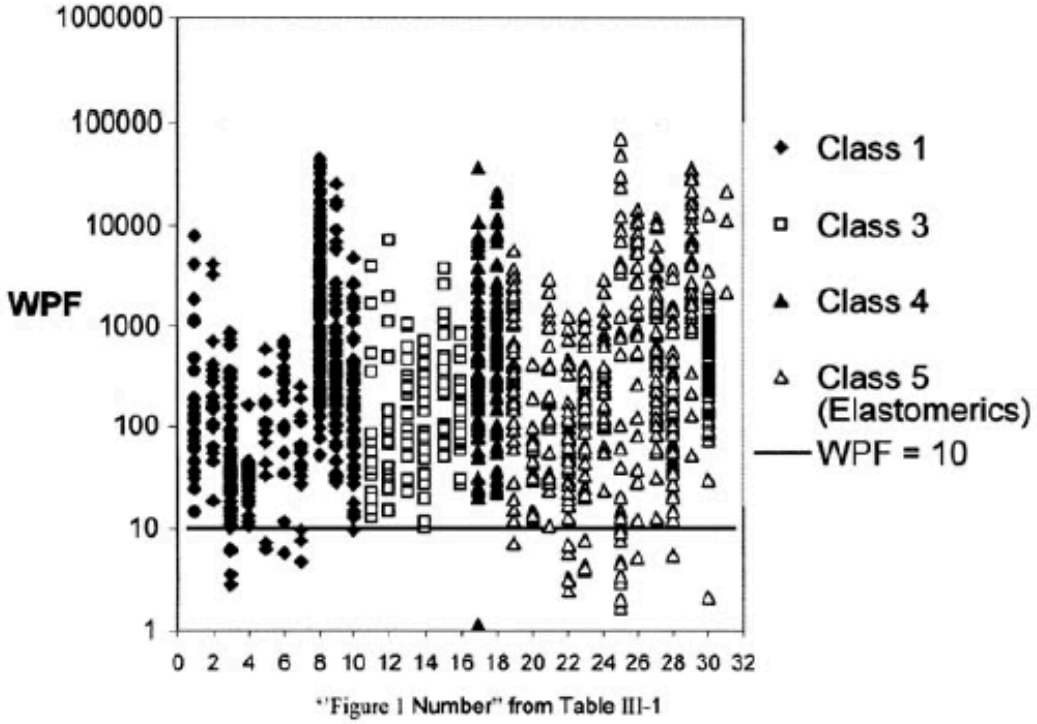
[3] This APF category includes filtering facepieces, and half masks with elastomeric facepieces.

[4] The employer must have evidence provided by the respirator manufacturer that testing of these respirators demonstrates performance at a level of protection of 1,000 or greater to receive an APF of 1,000. This level of performance can best be demonstrated by performing a WPF or SWPF study or equivalent testing. Absent such testing, all other PAPRs and SARs with helmets/hoods are to be treated as loose-fitting facepiece respirators, and receive an APF of 25.

[5] These APFs do not apply to respirators used solely for escape. For escape respirators used in association with specific substances covered by 29 CFR 1910 subpart Z, employers must refer to the appropriate substance-specific standards in that subpart. Escape respirators for other IDLH atmospheres are specified by 29 CFR 1910.134(d)(2)(ii).

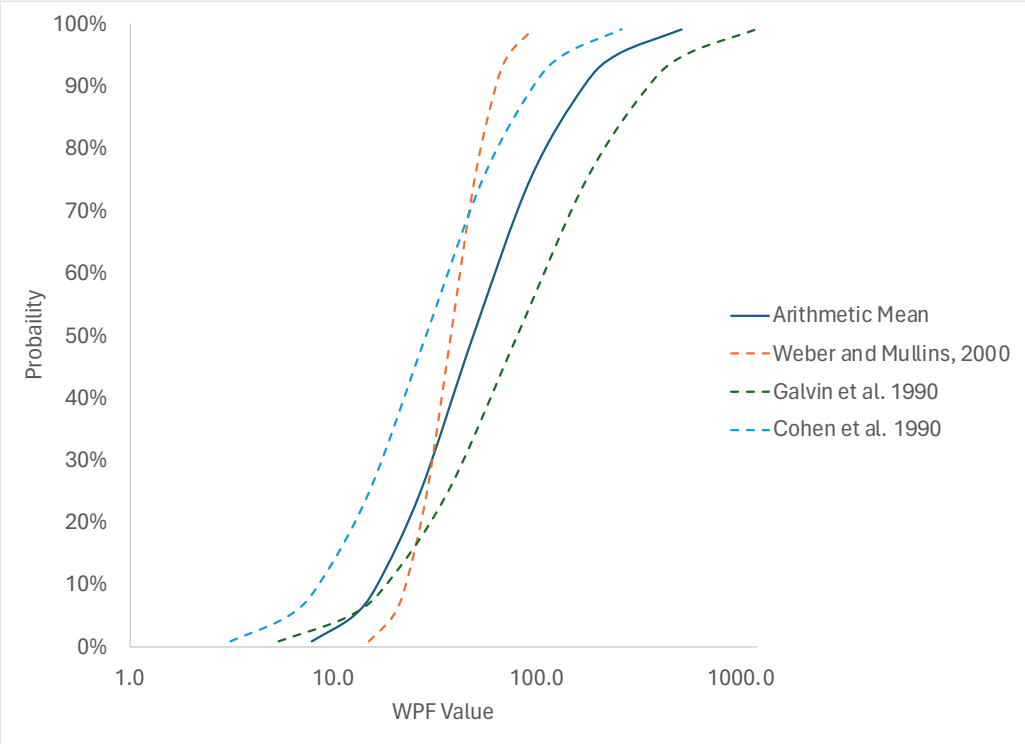
- The APF values are considered to be applicable for particulate, aerosol, or vapor exposures. For the half-face air purifying respiratory (APR), full-face APR, and supplied air respirators used by BD manufacture workers (**Table 3-4**), APF values of 10, 50, and 1000, respectively, are considered appropriate.
- WPF value can vary over a very wide range of possible values (e.g., from a value of approximately 1 to more than 100,000 depending upon conditions and respirator class; **Figure 3-2**; OSHA 2006). The data used in this figure do not appear to be readily available from OSHA's website.

Figure 3-2. Variation in Worker Protection Factors (from OSHA, 2006)



- For the purpose of predicting BD exposures (and associated hazards and risks) to U.S. workers, characterizations of variation in WPFs are available in the published literature (Nicas and Neuhaus, 2004; Crump, 2007), which have focused on data for half-mask air purifying respirators (best studied class of respirator). Both publications cite three papers that specifically characterize variation in WPF values specifically for vapor exposures (Cohen et al. 1984; Galvin et al. 1990; Weber and Mullins, 2000). The variation in WPF values (combined for within- and between- worker) from these studies is modeled as lognormally distributed (**Figure 3-3**), from which a composite distribution (based on arithmetic mean of percentile values across studies) was generated. Note that the combining of within- and between- variation was performed to be consistent with the treatment of other exposure parameters in a 1-dimensional Monte Carlo risk assessment (refinements to treat sources of variation separately may be considered in follow-up work for this risk assessment). The 5th percentile for the composite distribution (12.5) corresponds reasonably well with the nominal protection factor of 10 for this respirator category.

Figure 3-3. Cumulative Probability Density Function for WPF Values for Half-Mask Respirators



- 29 CFR 1910.134, OSHA Respiratory Protection Standard requires "All employees using a negative or positive pressure tight-fitting facepiece respirator must pass an appropriate qualitative fit test (QLFT) or quantitative fit test (QNFT). Fit testing is required prior to initial use, whenever a different respirator facepiece is used, and at least annually thereafter. An additional fit test is required whenever the employee reports, or the employer or PLHCP makes visual observations of, changes in the employee's physical condition that could affect respirator fit (e.g., facial scarring, dental changes, cosmetic surgery, or an obvious change in body weight).", in addition to medical evaluation and training. Therefore, it is expected that the WPF for individual workers are higher than the APF.
- Similar WPF data for vapor exposures are not readily available for full-face air purifying respirators to characterize their variation. Instead, it is proposed that the distribution of WPF values for half-masked respirators are adopted for the full-face respirator category, but are shifted to the right by a factor of 5 (based on the proportion of their APF values of 50 and 10).
- For supplied air respirators (SARs), the study of Cohen et al. (2001) was used to define a distribution of WPF values. In this study 6 SARs were evaluated, of which five performed well, with the median WPF values greater than 250,000 (limit of detection) (**Table 3-5**). One respirator (SAR5 in **Table 3-5**) performed poorly and was highly variable (WPF values ranging from 5 to >250,000). The performance of this respirator improved

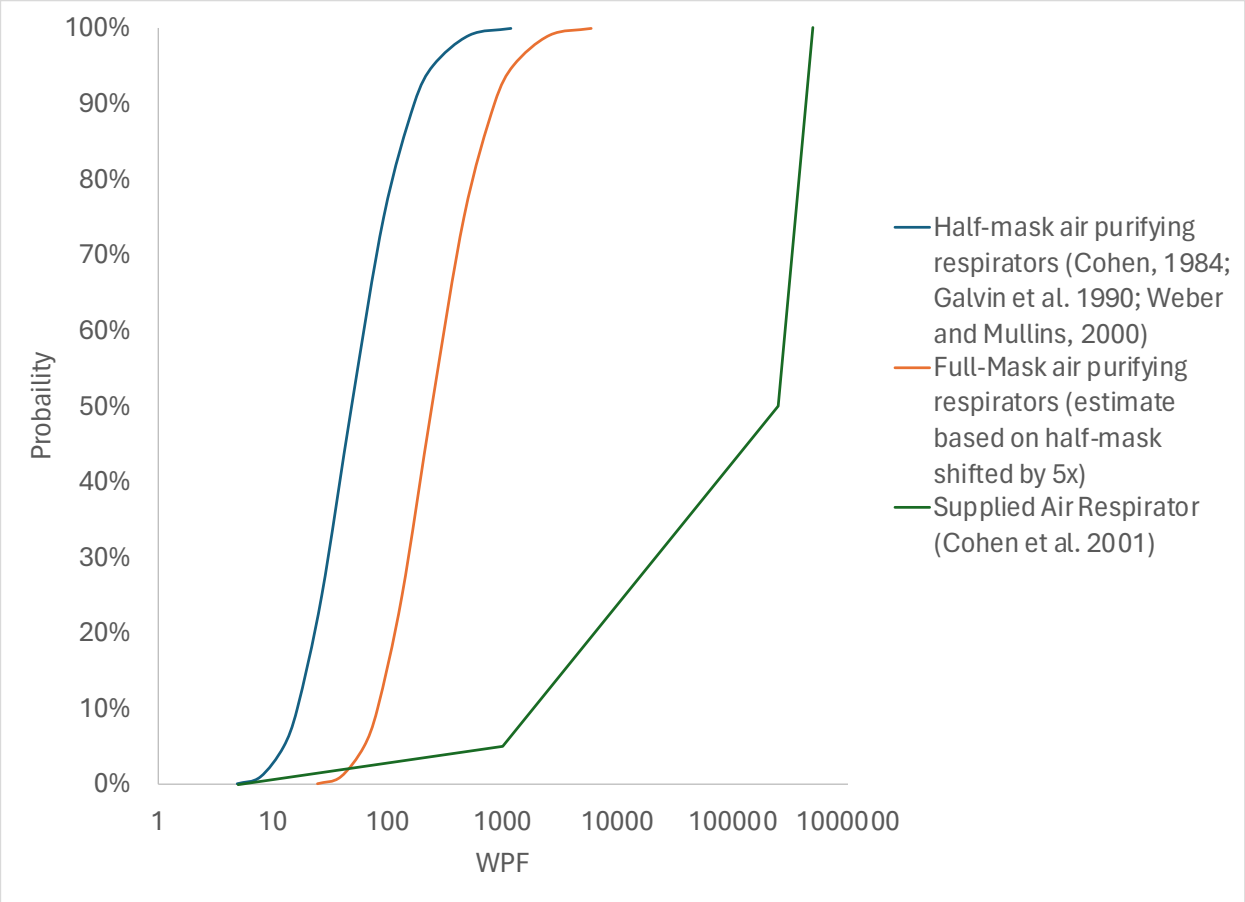
greatly when it was used with a bib. Based on these results, variation in the WPF for SARs is proposed to be defined as broader custom distribution with the left tail extended to include the possibility of poor performing respirators: 5% probability between a value of 5 (minimum for the poor fitting SAR) to 1000 (nominal APF for the respirator category; 45% probability between 1000 and 250,000 (conservative estimate of the median WPF); and a 50% probability between 250,000 and 500,000 (assumed high-end limit).

Table 3-5. Simulated Workplace Protection Factors for Supplied Air Respirators (SARs) and Powered Air Purifying Respirators (PAPRs) (Cohen et al. 2001).

Device	Range of SWPFs	Median SWPF	5th Percentile SWPF
PAPR1	140,000–>250,000	>250,000	>250,000
PAPR2	11,000–>250,000	>250,000	170,000–210,000
PAPR3	11,000–>250,000	>250,000	>250,000
PAPR4	94,000–>250,000	>250,000	246,000–>250,000
PAPR5	240–>250,000	>250,000	150,000–230,000
SAR1	68,000–>250,000	>250,000	>250,000
SAR2	13,000–>250,000	>250,000	170,000–220,000
SAR3	9700–>250,000	>250,000	86,000–114,000
SAR4	55,000–>250,000	>250,000	150,000–240,000
SAR5	5–>250,000	GM = 1217	13–18
SAR6	160,000–>250,000	>250,000	>250,000

- Resulting cumulative distributions for the three respirator categories are depicted in **Figure 3-4**, and together the three distributions do a reasonable job of capturing the range of WPF values depicted in **Figure 3-1** for OSHA's database used to define APF values and depicted in **Table 3-5**.

Figure 3-4. Cumulative Probability Density Function for WPF Values for Full-Mask and Supplied Air Respirators Estimated from the Distribution for Half-Mask Respirators



- The WPF distributions in **Figure 3-4** are proposed for application in the BD risk assessment to characterize variation in the degree of protection offered by different respirator types when predicting BD exposures to workers. Risk calculations for exposed workers will also be performed assuming no respirator use. In this way, each occupational exposure scenario in the risk assessment will include 4 evaluations for the different respirator assumptions to provide coverage across a wide range of situations that may be encountered across industries/companies.

3.6. Aggregate Exposures

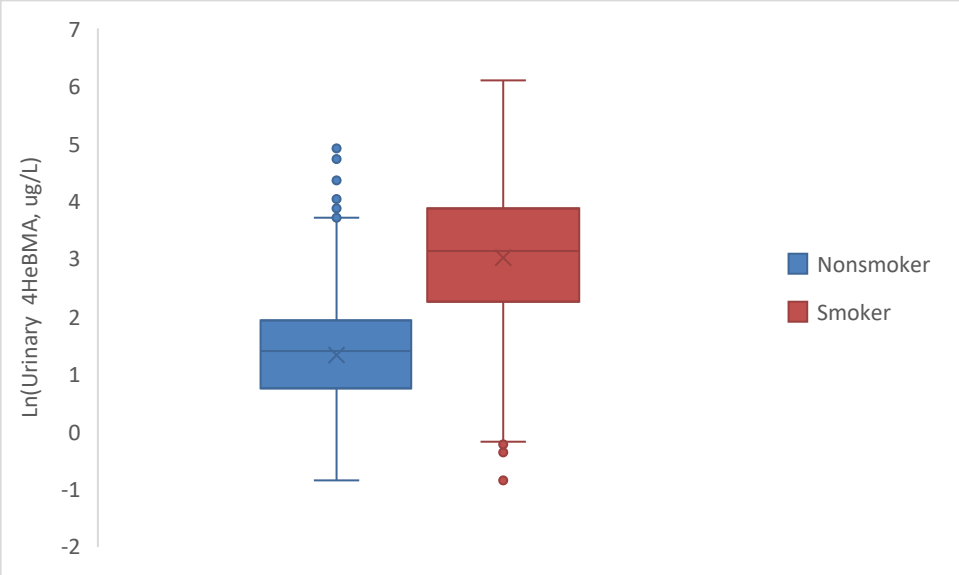
- The potential noncancer hazards and risks for several aggregated exposure scenarios will be considered in the risk assessment for BD, including the following:

Aggregate 1 = [Ambient Air]+[In-vehicle Air]+[Indoor Air]
Aggregate 2 = [Ambient Air] [In-vehicle Air]+[Indoor Air]+[Workplace Air]
Aggregate 3 = [Ambient Air]+[In-vehicle Air]+[Indoor Air]+[Smoking]
Aggregate 4 = [Ambient Air]+[In-vehicle Air]+[Indoor Air]+[Workplace Air]+[Smoking]

- Ambient air exposures to BD will be characterized using air concentration distributions defined for the locations in Houston, TX as an upper-bound characterization for this pathway (see Round 3 Summary Report).
- Workplace air exposures to BD will be characterized using air concentration distributions defined for BD manufacturing workers (Safety Health and Engineering) as an upper-bound characterization for this pathway (see Round 3 Summary Report).
- Exposure times for ambient air, in-vehicle, and workplace air will be defined as described in the Round 3 Summary Report, as modified by panel input. Exposure time to indoor air will be adjusted based on a consideration of the other pathways [i.e., 24 hours – sum(other exposure times)] to ensure that the sum of exposure times equals 24 hours/day.
- Exposures to BD via smoking will be estimated indirectly by making use of NHANES biomarker data for BD (urinary N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine or 4HeBMA (Nieto et al. 2021) in smokers and nonsmokers. Please note the use of the term "indirect estimate" is used here in place of the term "semi-quantitative" calculations in the summary material used in previous rounds that resulted in some confusion. Urinary 4HeBMA for smokers and nonsmokers from NHANES (2011-2018) are depicted in **Figure 3-5**. Based on a consideration of the ratio of the means for smokers and nonsmokers (35.4 ug/L / 5.6 ug/L = ~6.4), total exposures to BD in U.S. smokers are estimated to be ~6.4-fold higher than BD exposures in nonsmokers (i.e. smoking contributes a 5.4-fold excess of BD exposure over background). Under an assumption that U.S. nonsmoker exposures to BD are approximately equivalent to exposures calculated for Aggregate 1, the added BD exposures to U.S. smokers can be estimated as follows:

Smoking equivalent ppm = [Aggregate 1] x (6.4 - 1)

Figure 3-5. BD Urinary Biomarker (4HEBMA) in Smokers and Nonsmokers (NHANES 2011-18)



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Vacek PM, Albertini RJ, Sram RJ, Upton P, Swenberg JA. Hemoglobin adducts in 1,3-butadiene exposed Czech workers: female-male comparisons. Chem Biol Interact. 2010 Dec 5;188(3):668-76. doi: 10.1016/j.cbi.2010.06.017. Epub 2010 Jul 7. PMID: 20619252.

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BD Systematic Review Searches

PubMed search syntax:

(("1,3-butadiene" OR 106-99-0 OR "1,3 butadiene" OR "1,3-butadiene" [Supplementary Concept]) OR (butenediol OR 1,2,3,4-diepoxybutane OR butadiene diepoxide OR 3,4-epoxy-1-butene OR epoxybutene OR 1,2-epoxybutene OR epoxybutane diol OR 1,2-dihydroxy-3,4-epoxybutane OR hydroxymethylvinyl ketone OR "N-(2-hydroxy-3-butenyl)-valine" OR "1,2-dihydroxy-4-(N-acetylcysteinyl)-butane" OR "1-(N-acetylcysteinyl)-2-hydroxy-3-butene" OR "N,N-(2,3-dihydroxy-1,4-butadiyl)-valine" OR "N-(2,3,4-trihydroxybutyl)-valine" OR "N7-(1-hydroxy-3-buten-2-yl) guanine" OR 4-vinylcyclohexene OR 203-450-8 OR buta-1,3-diene OR butadien)) AND (safe OR safety OR toxic OR toxicity OR NOAEL OR LD50 OR LC50 OR "consumer product safety"[MeSH Terms] OR "Toxicity Tests"[MeSH Terms] OR tox[sb] OR absorption OR distribution OR metabolism OR excretion OR ADME[tiab] OR allergy OR allergen OR allergenicity OR allergic OR allergens[MeSH Terms] OR sensitiz* OR "hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "allergy and immunology"[MeSH Terms] OR atopic[All Fields] OR (toxicity AND (development OR developmental OR reproductive)) OR "Teratogenesis"[MeSH Terms] OR teratogen OR teratogenic OR neoplastic OR cancer OR carcinogen* OR carcinoma OR tumor OR tumors OR "animal bioassay" OR oncogenic* OR malignant OR malignancy OR malignancies OR cancer[sb] OR genotoxic OR genotoxicity OR clastogen* OR mutagen OR mutagenic OR mutation* OR "cytogenetic aberration" OR "chromosome aberrations"[MeSH Terms] OR micronucle* OR "DNA damage" OR "DNA fragmentation"[Mesh] OR "Mutagenicity Tests"[MeSH Terms] OR "comet assay" OR "ecotoxicology"[MeSH] OR exposure OR exposed OR manufactur* OR processing OR disposal OR waste OR consumer OR worker OR "Occupational Exposure"[Mesh] OR "Inhalation Exposure"[Mesh] OR population OR "air quality" OR "indoor air")

Embase search syntax:

('1,3 butadiene'/exp OR '1,3 butadiene' OR 106-99-0 OR butenediol OR '1,2,3,4-diepoxybutane'/exp OR '1,2,3,4-diepoxybutane' OR 'butadiene diepoxide'/exp OR 'butadiene diepoxide' OR '3,4-epoxy-1-butene'/exp OR '3,4-epoxy-1-butene' OR epoxybutene OR '1,2-epoxybutene' OR 'epoxybutane diol' OR '1,2-dihydroxy-3,4-epoxybutane' OR 'n-(2-hydroxy-3-butenyl)-valine' OR 'hydroxymethylvinyl ketone' OR '1,2-dihydroxy-4-(n-acetylcysteinyl)-butane' OR '1-(n-acetylcysteinyl)-2-hydroxy-3-butene' OR 'n,n-(2,3-dihydroxy-1,4-butadiyl)-valine' OR 'n-(2,3,4-trihydroxybutyl)-valine' OR 'n7-(1-hydroxy-3-buten-2-yl) guanine' OR 4-vinylcyclohexene OR 203-450-8 OR buta-1,3-diene OR butadien) AND ('safety'/exp OR 'safety' OR 'toxic substance'/exp OR 'toxicity'/exp OR 'toxicity' OR ld50 OR 'lc50' OR 'malignant neoplasm'/exp OR 'product safety'/exp OR 'product safety' OR 'pharmacokinetics'/exp OR 'pharmacokinetics' OR 'metabolism'/exp OR 'metabolism' OR 'excretion'/exp OR 'excretion' OR 'exposure'/exp OR 'occupational exposure'/exp OR 'indoor air' OR manufactur* OR processing OR disposal OR waste OR 'ecotoxicity'/exp)

Initial Literature Search Results Conducted in 2020

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Lewis L, Borowa-Mazgaj B, de Conti A, et al. Population-Based Analysis of DNA Damage and Epigenetic Effects of 1,3-Butadiene in the Mouse. Chem Res Toxicol. 2019;32(5):887-898. doi:10.1021/acs.chemrestox.9b00035	2019	X	X					X	
Lewis L, Chappell GA, Kobets T, et al. Sex-specific differences in genotoxic and epigenetic effects of 1,3-butadiene among mouse tissues. Arch Toxicol. 2019;93(3):791-800. doi:10.1007/s00204-018-2374-x	2019	X	X				X		
Piccoli BC, Segatto ALA, Oliveira CS, D'Avila da Silva F, Aschner M, da Rocha JBT. Simultaneous exposure to vinylcyclohexene and methylmercury in Drosophila melanogaster: biochemical and molecular analyses. BMC Pharmacol Toxicol. 2019;20(Suppl 1):83. Published 2019 Dec 19. doi:10.1186/s40360-019-0356-0	2019	X		X			X		
Waczuk EP, Wagner R, Klein B, da Rocha JBT, Ardisson-Araújo DMP, Barbosa NV. Assessing the toxicant effect of spontaneously volatilized 4-vinylcyclohexane exposure in nymphs of the lobster cockroach nauphoeta cinerea. Environ Toxicol Pharmacol. 2019;72:103264. doi:10.1016/j.etap.2019.103264	2019								survival rate
Israel JW, Chappell GA, Simon JM, et al. Tissue- and strain-specific effects of a genotoxic carcinogen 1,3-butadiene on chromatin and transcription. Mamm Genome. 2018;29(1-2):153-167. doi:10.1007/s00335-018-9739-6	2018		X					X	
Wang Y, Yu YX, Luan Y, An J, Yin DG, Zhang XY. Bioactivation of 1-chloro-2-hydroxy-3-butene, an in vitro metabolite of 1,3-butadiene, by rat liver microsomes. Chem Biol Interact. 2018;282:36-44. doi:10.1016/j.cbi.2018.01.006	2018		X				X	X	
Chang SC, Seneviratne UI, Wu J, Tretyakova N, Essigmann JM. 1,3-Butadiene-Induced Adenine DNA Adducts Are Genotoxic but Only Weakly Mutagenic When Replicated in Escherichia coli of Various Repair and Replication Backgrounds. Chem Res Toxicol. 2017;30(5):1230-1239. doi:10.1021/acs.chemrestox.7b00064	2017	X	X				X	X	
Chappell GA, Israel JW, Simon JM, et al. Variation in DNA-Damage Responses to an Inhalational Carcinogen (1,3-Butadiene) in Relation to Strain-Specific Differences in Chromatin Accessibility and Gene Transcription Profiles in C57BL/6J and CAST/EiJ Mice. Environ Health Perspect. 2017;125(10):107006. Published 2017 Oct 16. doi:10.1289/EHP1937	2017	X	X				X		

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Hartman JH, Miller GP, Caro AA, et al. 1,3-Butadiene-induced mitochondrial dysfunction is correlated with mitochondrial CYP2E1 activity in Collaborative Cross mice. Toxicology. 2017;378:114-124. doi:10.1016/j.tox.2017.01.005	2017		X				X	X	
Hartman JH, Miller GP, Caro AA, et al. 1,3-Butadiene-induced mitochondrial dysfunction is correlated with mitochondrial CYP2E1 activity in Collaborative Cross mice. Toxicology. 2017;378:114-124. doi:10.1016/j.tox.2017.01.005	2016	X					X		
Noël A, Xiao R, Perveen Z, et al. Incomplete lung recovery following sub-acute inhalation of combustion-derived ultrafine particles in mice. Part Fibre Toxicol. 2016;13:10. Published 2016 Feb 24. doi:10.1186/s12989-016-0122-z	2016	X		X			X		
Dong J, Wang Z, Zou P, et al. Induction of DNA damage and G2 cell cycle arrest by diepoxybutane through the activation of the Chk1-dependent pathway in mouse germ cells. Chem Res Toxicol. 2015;28(3):518-531. doi:10.1021/tx500489r	2015		X	X			X	X	
Abolaji AO, Kamdem JP, Lugokenski TH, et al. Involvement of oxidative stress in 4-vinylcyclohexene-induced toxicity in Drosophila melanogaster [published correction appears in Free Radic Biol Med. 2015 May;82:204-5]. *Free Radic Biol Med* . 2014;71:99-108. doi:10.1016/j.freeradbiomed.2014.03.014	2014	X	X	X			X	X	
Abolaji AO, Kamdem JP, Lugokenski TH, et al. Involvement of oxidative stress in 4-vinylcyclohexene-induced toxicity in Drosophila melanogaster [published correction appears in Free Radic Biol Med. 2015 May;82:204-5]. Free Radic Biol Med. 2014;71:99-108. doi:10.1016/j.freeradbiomed.2014.03.014	2014	X		X			X		
Chappell G, Kobets T, O'Brien B, et al. Epigenetic events determine tissue-specific toxicity of inhalational exposure to the genotoxic chemical 1,3-butadiene in male C57BL/6J mice. Toxicol Sci. 2014;142(2):375-384. doi:10.1093/toxsci/kfu191	2014	X	X						
Kotapati S, Sangaraju D, Esades A, et al. Bis-butanediol-mercapturic acid (bis-BDMA) as a urinary biomarker of metabolic activation of butadiene to its ultimate carcinogenic species. Carcinogenesis. 2014;35(6):1371-1378. doi:10.1093/carcin/bgu047	2014							X	

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Sangaraju D, Villalta PW, Wickramaratne S, Swenberg J, Tretyakova N. NanoLC/ESI+ HRMS3 quantitation of DNA adducts induced by 1,3-butadiene [published correction appears in J Am Soc Mass Spectrom. 2014 Sep;25(9):1674]. J Am Soc Mass Spectrom. 2014;25(7):1124-1135. doi:10.1007/s13361-014-0916-x	2014		X				X	X	
Cho SH, Guengerich FP. In vivo roles of conjugation with glutathione and O6-alkylguanine DNA-alkyltransferase in the mutagenicity of the bis-electrophiles 1,2-dibromoethane and 1,2,3,4-diepoxybutane in mice. Chem Res Toxicol. 2013;26(11):1765-1774. doi:10.1021/tx4003534	2013		X				X	X	
Pianalto KM, Hartman JH, Boysen G, Miller GP. Differences in butadiene adduct formation between rats and mice not due to selective inhibition of CYP2E1 by butadiene metabolites. Toxicol Lett. 2013;223(2):221-227. doi:10.1016/j.toxlet.2013.08.025	2013	X	X				X	X	
Cho SH, Guengerich FP. Conjugation of butadiene diepoxide with glutathione yields DNA adducts in vitro and in vivo. Chem Res Toxicol. 2012;25(3):706-712. doi:10.1021/tx200471x	2012		X				X	X	
Millard JT, McGowan EE, Bradley SQ. Diepoxybutane interstrand cross-links induce DNA bending. Biochimie. 2012;94(2):574-577. doi:10.1016/j.biochi.2011.07.030	2012		X				X	X	
Sangaraju D, Goggin M, Walker V, Swenberg J, Tretyakova N. NanoHPLC-nanoESI(+)-MS/MS quantitation of bis-N7-guanine DNA-DNA cross-links in tissues of B6C3F1 mice exposed to subppm levels of 1,3-butadiene. Anal Chem. 2012;84(3):1732-1739. doi:10.1021/ac203079c	2012		X					X	
Csanády GA, Steinhoff R, Riester MB, et al. 1,2:3,4-Diepoxybutane in blood of male B6C3F1 mice and male Sprague-Dawley rats exposed to 1,3-butadiene. Toxicol Lett. 2011;207(3):286-290. doi:10.1016/j.toxlet.2011.09.027	2011							X	
Goggin M, Sangaraju D, Walker VE, Wickliffe J, Swenberg JA, Tretyakova N. Persistence and repair of bifunctional DNA adducts in tissues of laboratory animals exposed to 1,3-butadiene by inhalation. Chem Res Toxicol. 2011;24(6):809-817. doi:10.1021/tx200009b	2011	X	X					X	

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Goggin M, Sangaraju D, Walker VE, Wickliffe J, Swenberg JA, Tretyakova N. Persistence and repair of bifunctional DNA adducts in tissues of laboratory animals exposed to 1,3-butadiene by inhalation. Chem Res Toxicol. 2011;24(6):809-817. doi:10.1021/tx200009b	2011	X	X					X	
Kim MY. Genotoxicity of stereoisomers of 1,2,3,4-diepoxybutane in the gpt gene of Chinese hamster ovary AS52 cells. Bull Environ Contam Toxicol. 2011;86(6):587-590. doi:10.1007/s00128-011-0280-5	2011		X				X	X	
Koturbash I, Scherhag A, Sorrentino J, et al. Epigenetic alterations in liver of C57BL/6J mice after short-term inhalational exposure to 1,3-butadiene. Environ Health Perspect. 2011;119(5):635-640. doi:10.1289/ehp.1002910	2011		X						hepatotoxicity
Koturbash I, Scherhag A, Sorrentino J, et al. Epigenetic mechanisms of mouse interstrain variability in genotoxicity of the environmental toxicant 1,3-butadiene. Toxicol Sci. 2011;122(2):448-456. doi:10.1093/toxsci/kfr133	2011		X				X		
Georgieva, NL, G Boysen, Bordeerat N, Walker VE and Swenberg JA. (2010). Exposure-response of 1,2:3,4-diepoxybutane-specific N-terminal valine adducts in mice and rats after inhalation exposure to 1,3-butadiene.Toxicol Sci,115, 322-329.	2010							X	
Filser JG, Hutzler C, Meischner V, et al. 2007. Metabolism of 1,3-butadiene to toxicologically relevant metabolites in single-exposed mice and rats. Chem Biol Interact 166(1-3):93-103.	2007							X	
Kligerman, AD and Y Hu. 2007. Some insights into the mode of action of butadiene by examining the genotoxicity of its metabolites. Chem Biol Inter 166: 132-139.	2007			X				X	
Swenberg JA, Boysen G, Georgieva N, Bird MG, Lewis RJ. (2007). Future directions in butadiene risk assessment and the role of cross-species internal dosimetry. Chem Biol Interact. 166: 78-83.	2007							X	
Slikker, Jr, W, ME Andersen, MS Bogdanffy, et al. 2004. Dose-dependent transitions in mechanisms of toxicity: Case studies. Tox Appl Pharm 201: 226-94.	2004							X	
Zocchetti C, Pesatori AC, Bertazzi PA. (2004) [A simple method for risk assessment and its application to 1,3-butadiene]. Med Lav. 95(5), 392-409	2004	X							

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
American Chemistry Council (ACC). 2003. An inhalation reproduction/developmental toxicity screening study of 1,3-butadiene in rats. WIL Research Laboratories. OLF-68.0-BDHPV-WIL.	2003					X			
Green, JW. 2003. Statistical analysis of butadiene mouse data from Hackett et al. (1987) for American Chemistry Council. Laboratory Project ID: Dupont-13474. Sponsor Contract ID: OLF-114.0-BD-stat-DHL. pp 1-151.	2003					X			
Swain CM, Booth ED, Watson WP. 2003. Metabolic distribution of radioactivity in Sprague-Dawley rats and B6C3F1 mice exposed to 1,3-[2,3-14C]-butadiene by whole body exposure. Chem Biol Interact 145:175-189.	2003							X	
Unnamed study report. 2003. (as cited in ECHA)	2003					X			
WIL, 2003 (as cited in ECHA)	2003					X			
Chi, L, E Nixon, and F Spencer. 2002. Uterine-ovarian biochemical and developmental interactions to the postimplantation treatment with a butadiene metabolite, diepoxybutane, in pregnant rats. J Biochem Molecular Toxicology 16: 147-153.	2002								
Filser JG, Faller TH, Bhowmik S, et al. 2001. First-pass metabolism of 1,3-butadiene in once-through perfused livers of rats and mice. Chem Biol Interact 135-136:249-265.	2001							X	
Kohn MC, Melnick RL. 2001. Physiological modeling of butadiene disposition in mice and rats. Chem Biol Interact 135-136:285-301.	2001							X	
Sills RC, Hong HL, Boorman GA, et al. 2001. Point mutations of K-ras and H-ras genes in forestomach neoplasms from control B6C3F1 mice and following exposure to 1,3-butadiene, isoprene or chloroprene for up to 2-years. Chem Biol Interact 135-136:373-386.	2001		X						
Spencer, F, L Chi, and M Zhu. 2001. A mechanistic assessment of 1,3-butadiene diepoxideinduced inhibition of uterine deciduoma proliferation in pseudopregnant rats. Reprod Toxicol 15: 253-60.	2001								
Koc, H; Tretyakova, NY; Walker, VE; et al. (1999) Molecular dosimetry of N-7 guanine adduct formation in mice and rats exposed to 1,3-butadiene. Chem Res Toxicol 12:566-574.	1999	X						X	

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Anderson D, Hughes JA, Edwards AJ, et al. 1998. A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutat Res 397(1):77-84.	1998					X			
Hackett (1998)	1998					X			
NTP. (1997) NTP Technical Report on the toxicology and carcinogenesis studies of isoprene in F344/N rats. Technical Report No. 486 (Draft), U.S. DHHS.	1998	X						X	
Anderson D, Edwards AJ, Brinkworth MH, et al. 1996. Male-mediated F1 effects in mice exposed to 1,3-butadiene. Toxicology 113(1-3):120-127.	1996					X			
Bevan C, Stadler JC, Elliott GS, et al. 1996. Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. Fundam Appl Toxicol 32(1):1-10.	1996					X			
Doerr, JK, EA Hollis, and IG Sipes. (1996). Species difference in the ovarian toxicity of 1,3-butadiene epoxides in B6C3F1 mice and Sprague-Dawley rats. Toxicology 113:128-36.	1996								
Doerr et al, 1995 (as cited in ECHA)	1995								
Melnick, RL; Kohn, MC. (1995) Mechanistic data indicate that 1,3-butadiene is a human carcinogen. Carcinogenesis 16(2):157-163.	1995	X						X	
Thornton-Manning JR, Dahl AR, Bechtold WE, et al. 1995a. Disposition of butadiene monoepoxide and butadiene diepoxide in various tissues of rats and mice following a low-level inhalation exposure to 1,3-butadiene. Carcinogenesis 16(8):1723-1731.	1995							X	
Himmelstein MW, Turner MJ, Asgharian B, et al. 1994. Comparison of blood concentrations of 1,3-butadiene and butadiene epoxides in mice and rats exposed to 1,3-butadiene by inhalation. Carcinogenesis 15(8):1479-1486.	1994							X	
Bucher (1993) (as cited in ECHA)	1993	X							
NTP. 1993. NTP technical report on the toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 434.	1993	X	X			X			Renal effects; musculoskeletal effects; cardiovascular effects; eye irritation
Dahl AR, Bechtold WE, Bond JA, et al. 1990. Species differences in the metabolism and disposition of inhaled 1,3-butadiene and isoprene. Environ Health Perspect 86:65-69.	1990							X	

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Melnick RL, Huff J, Chou BJ, et al. 1990a. Carcinogenicity of 1,3-butadiene in C57BL/6 x C3H F1 mice at low exposure concentrations. Cancer Res 50(20):6592-6599.	1990								
Owen PE, Glaister JR. 1990. Inhalation toxicity and carcinogenicity of 1,3-butadiene in Sprague-Dawley rats. Environ Health Perspect 86:19-25.	1990	X			X				
DOE/NTP. 1988a. Sperm-head morphology study in B6C3F1 mice following inhalation exposure to 1,3-butadiene. Final technical report. Richland, WA: U.S. Department of Energy. National Toxicology Program. PNL6459. DE88008620.	1988					X			
Bond JA, Dahl AR, Henderson RF, et al. 1987. Species differences in the distribution of inhaled butadiene in tissues. Am Ind Hyg Assoc J 48(10):867-872.	1987							X	
DOE/NTP. 1987a. Inhalation developmental toxicology studies of 1,3-butadiene in the rat. Final report. Richland, WA: U.S. Department of Energy. National Toxicology Program. PNL6414. DE88004186.	1987					X			
DOE/NTP. 1987b. Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice. Final report. U.S. Department of Energy. National Toxicology Program. PNL6412. DE88004187.	1987					X			
Hackett, PL, MR Sikov, TJ Mast, et al. 1987a. Inhalation developmental toxicology studies of 1,3-butadiene in the rat (final report). Richland, W.A.: Pacific Northwest Laboratory; PNL Report No. PNL-6414 UC-48; NIH Report No. NIH- 401-ES-41031l 101 p. Prepared for NIEHS, NTP, under a Related Services Agreement with the U.S. Department of Energy under contract DE-AC06-76RLO-1830.	1987					X			
Hackett, PL, MR Sikov, TJ Mast, et al. 1987b. Inhalation developmental toxicology studies: Teratology study of 1,3-butadiene in mice (final report). Richland, W.A.: Pacific Northwest Laboratory; PNL Report No. PNL-6412 UC-48; NIH Report No. NIH- 401-ES-41031l 92 p. Prepared for NIEHS, NTP, under a Related Services Agreement with the U.S. Department of Energy under contract DE-AC06-76RLO-1830.	1987					X			
Owen PE, Glaister JR, Gaunt IF, Pullinger DH. 1987. Inhalation toxicity studies with 1,3-butadiene. 3. Two year toxicity/carcinogenicity study in rats. Am Ind Hyg Assoc J. 48; 407-413.	1987	X			X	X			Renal effects; cardiovascular effects; eye irritation

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Bond JA, Dahl AR, Henderson RF, et al. 1986. Species differences in the disposition of inhaled butadiene. Toxicol Appl Pharmacol 84(3):617-627.	1986							X	
Irons RD, Smith CN, Stillman WS, et al. 1986a. Macrocytic-megaloblastic anemia in male B6C3F1 mice following chronic exposure to 1,3-butadiene. Toxicol Appl Pharmacol 83(1):95-100.	1986								
Irons RD, Smith CN, Stillman WS, et al. 1986b. Macrocytic-megaloblastic anemia in male NIH Swiss mice following repeated exposure to 1,3-butadiene. Toxicol Appl Pharmacol 85(3):450-455.	1986	X							
Thurmond LM, Lauer LD, House RV, et al. 1986. Effect of short-term inhalation exposure to 1,3-butadiene on murine immune functions. Toxicol Appl Pharmacol 86(2):170-179.	1986			X					
NTP. 1984. NTP toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program.	1984	X			X	X			Renal effects; musculoskeletal effects; cardiovascular effects; eye irritation
Unnamed study report. 1982. (as cited in ECHA)	1982					X			
Hazleton Laboratories Europe Ltd. (1981) The toxicity and carcinogenicity of butadiene gas administered to rats by inhalation for approximately 24 months. Prepared for the International Institute of Synthetic Rubber Producers, New York, NY. Unpublished.	1981	X							
Irvine LFH. 1981. 1,3-Butadiene: Inhalation teratogenicity study in the rat. Final report. Harrogate, England: Hazleton Laboratories Europe Ltd. OTS050545.	1981					X			
Crouch CN, Pullinger DH, Gaunt IF. 1979. Inhalation toxicity studies with 1,3-butadiene 2. 3 month toxicity study in rats. Am Ind Hyg Assoc J 40:796-802.	1979				X	X			Renal effects; musculoskeletal effects; cardiovascular effects; eye irritation
Shugaev B. 1969. Concentrations of hydrocarbons in tissues as a measure of toxicity. Arch. Environ. Health, 18, 878-882.	1969						X		

Animal studies: *in vivo* and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Immunotoxicity	Neurotoxicity	Reproductive or Developmental	Mechanistic	ADME	Other
Carpenter CP, Shaffer CB, Weir CS, Smyth HF. 1944. Studies on the inhalation of 1,3-butadiene; with a comparison of its narcotic effect with benzol, toluol and styrene, and a note on the elimination of styrene by the human. J Ind Hyg Toxicol 26; 69-78	1944				X	X			Renal effects; eye irritation
ACC Olefins Planel OECD 421 guideline study (reproductive and developmental toxicity screen) using BD of >99% purity.									
ACC Olefins Planel OECD 422 guideline study (reproductive and developmental toxicity screen) using crude 1,3-butadiene (containing 10% 1,3-butadiene)									

Human Studies: Epidemiological and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
Degner A, Arora R, Erber L, Chao C, Peterson LA, Tretyakova NY. Interindividual Differences in DNA Adduct Formation and Detoxification of 1,3-Butadiene-Derived Epoxide in Human HapMap Cell Lines [published online ahead of print, 2020 Apr 15]. Chem Res Toxicol. 2020;10.1021/acs.chemrestox.9b00517. doi:10.1021/acs.chemrestox.9b00517	2020		X	X	X	
Ewunkem AJ, Deve M, Harrison SH, Muganda PM. Diepoxybutane induces the expression of a novel p53-target gene XCL1 that mediates apoptosis in exposed human lymphoblasts. J Biochem Mol Toxicol. 2020;34(3):e22446. doi:10.1002/jbt.22446	2020		X	X	X	
Wen Y, Zhang PP, An J, et al. Diepoxybutane induces the formation of DNA-DNA rather than DNA-protein cross-links, and single-strand breaks and alkali-labile sites in human hepatocyte L02 cells. Mutat Res. 2011;716(1-2):84-91. doi:10.1016/j.mrfmmm.2011.08.007	2019		X	X	X	
Eluka-Okoludoh E, Ewunkem AJ, Thorpe S, Blanchard A, Muganda P. Diepoxybutane-induced apoptosis is mediated through the ERK1/2 pathway. Hum Exp Toxicol. 2018;37(10):1080-1091. doi:10.1177/0960327118755255	2018		X	X	X	
Groehler AS 4th, Najjar D, Pujari SS, Sangaraju D, Tretyakova NY. N6-(2-Deoxy-d- erythro-pentofuranosyl)-2,6-diamino-3,4-dihydro-4-oxo-5- N-(2-hydroxy-3-buten-1-yl)-formamidopyrimidine Adducts of 1,3-Butadiene: Synthesis, Structural Identification, and Detection in Human Cells. Chem Res Toxicol. 2018;31(9):885-897. doi:10.1021/acs.chemrestox.8b00123	2018		X	X	X	
Le PM, Silvestri VL, Redstone SC, Dunn JB, Millard JT. Cross-linking by epichlorohydrin and diepoxybutane correlates with cytotoxicity and leads to apoptosis in human leukemia (HL-60) cells. Toxicol Appl Pharmacol. 2018;352:19-27. doi:10.1016/j.taap.2018.05.020	2018		X	X	X	
Zhang PP, Wen Y, An J, Yu YX, Wu MH, Zhang XY. DNA damage induced by three major metabolites of 1,3-butadiene in human hepatocyte L02 cells. Mutat Res. 2012;747(2):240-245. doi:10.1016/j.mrgentox.2012.06.001	2018		X	X	X	
Liu LY, Zheng J, Kong C, et al. Characterization of the Major Purine and Pyrimidine Adducts Formed after Incubations of 1-Chloro-3-buten-2-one with Single-/Double-Stranded DNA and Human Cells. Chem Res Toxicol. 2017;30(2):552-563. doi:10.1021/acs.chemrestox.6b00282	2017		X	X	X	
Barajas Torres RL, Domínguez Cruz MD, Borjas Gutiérrez C, Ramírez Dueñas Mde L, Magaña Torres MT, González García JR. 1,2:3,4-Diepoxybutane Induces Multipolar Mitosis in Cultured Human Lymphocytes. Cytogenet Genome Res. 2016;148(2-3):179-184. doi:10.1159/000445858	2016		X	X	X	
Ye J, Farrington CR, Millard JT. Polymerase bypass of N7-guanine monoadducts of cisplatin, diepoxybutane, and epichlorohydrin. Mutat Res. 2018;809:6-12. doi:10.1016/j.mrfmmm.2018.03.002	2016		X	X		
Kotapati S, Wickramaratne S, Esades A, et al. Polymerase Bypass of N(6)-Deoxyadenosine Adducts Derived from Epoxide Metabolites of 1,3-Butadiene. Chem Res Toxicol. 2015;28(7):1496-1507. doi:10.1021/acs.chemrestox.5b00166	2015		X	X	X	

Human Studies: Epidemiological and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
Walker VE, Degner A, Carter EW, et al. 1,3-Butadiene metabolite 1,2,3,4 diepoxybutane induces DNA adducts and micronuclei but not t(9;22) translocations in human cells. Chem Biol Interact. 2019;312:108797. doi:10.1016/j.cbi.2019.108797	2015		X	X	X	
Fuccelli R, Sepporta MV, Rosignoli P, Morozzi G, Servili M, Fabiani R. Preventive activity of olive oil phenolic compounds on alkene epoxides induced oxidative DNA damage on human peripheral blood mononuclear cells. Nutr Cancer. 2014;66(8):1322-1330.	2014		X	X	X	
Hartman JH, Miller GP, Boysen G. Inhibitory potency of 4-carbon alkanes and alkenes toward CYP2E1 activity. Toxicology. 2014;318:51-58. doi:10.1016/j.tox.2014.02.003	2014		X	X	X	
Kowal EA, Wickramaratne S, Kotapati S, Turo M, Tretyakova N, Stone MP. Major groove orientation of the (2S)-N(6)-(2-hydroxy-3-buten-1-yl)-2'-deoxyadenosine DNA adduct induced by 1,2-epoxy-3-butene. Chem Res Toxicol. 2014;27(10):1675-1686. doi:10.1021/tx500159w	2014		X	X	X	
Sangaraju D, Villalta PW, Wickramaratne S, Swenberg J, Tretyakova N. NanoLC/ESI+ HRMS3 quantitation of DNA adducts induced by 1,3-butadiene [published correction appears in J Am Soc Mass Spectrom. 2014 Sep;25(9):1674]. J Am Soc Mass Spectrom. 2014;25(7):1124-1135. doi:10.1007/s13361-014-0916-x	2014		X	X	X	
Gherezghiher TB, Ming X, Villalta PW, Campbell C, Tretyakova NY. 1,2,3,4-Diepoxybutane-induced DNA-protein cross-linking in human fibrosarcoma (HT1080) cells. J Proteome Res. 2013;12(5):2151-2164. doi:10.1021/pr3011974	2013		X	X	X	
Liu XJ, Zeng FM, An J, Yu YX, Zhang XY, Elfarra AA. Cytotoxicity, genotoxicity, and mutagenicity of 1-chloro-2-hydroxy-3-butene and 1-chloro-3-buten-2-one, two alternative metabolites of 1,3-butadiene. Toxicol Appl Pharmacol. 2013;271(1):13-19. doi:10.1016/j.taap.2013.04.019	2013		X	X	X	
Fabiani R, Rosignoli P, De Bartolomeo A, Fuccelli R, Morozzi G. Genotoxicity of alkene epoxides in human peripheral blood mononuclear cells and HL60 leukaemia cells evaluated with the comet assay. Mutat Res. 2012;747(1):1-6. doi:10.1016/j.mrgentox.2012.01.004	2012		X	X	X	
Kotapati S, Maddukuri L, Wickramaratne S, et al. Translesion synthesis across 1,N6-(2-hydroxy-3-hydroxymethylpropan-1,3-diyl)-2'-deoxyadenosine (1,N6-γ-HMHP-dA) adducts by human and archebacterial DNA polymerases. J Biol Chem. 2012;287(46):38800-38811. doi:10.1074/jbc.M112.396788	2012		X	X	X	
Kotapati S, Maddukuri L, Wickramaratne S, et al. Translesion synthesis across 1,N6-(2-hydroxy-3-hydroxymethylpropan-1,3-diyl)-2'-deoxyadenosine (1,N6-γ-HMHP-dA) adducts by human and archebacterial DNA polymerases. J Biol Chem. 2012;287(46):38800-38811. doi:10.1074/jbc.M112.396788	2012		X	X	X	
Zhang S, Chen H, Wang A, Liu Y, Hou H, Hu Q. Genotoxicity evaluation of carbon monoxide and 1,3-butadiene using a new joint technology: the in vitro γH2AX HCS assay combined with air-liquid interface system. Toxicol Mech Methods. 2019;29(1):1-7. doi:10.1080/15376516.2018.1477897	2012		X	X	X	

Human Studies: Epidemiological and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
Dixon, Lea, and E. Martinez-Ceballos. "Role of DEB-Induced ROS Production During the Activation of Cell Survival Pathways in Prostate Cancer Cells." INTERNATIONAL JOURNAL OF TOXICOLOGY. Vol. 30. No. 1. 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA: SAGE PUBLICATIONS INC, 2011.	2011		X	X	X	
Wickramaratne S, Banda DM, Ji S, et al. Base Excision Repair of N6-Deoxyadenosine Adducts of 1,3-Butadiene. Biochemistry. 2016;55(43):6070-6081. doi:10.1021/acs.biochem.6b00553	2011		X	X	X	
Sathiakumar N, Tipre M, Leader M, Brill I, Delzell E. Mortality Among Men and Women in the North American Synthetic Rubber Industry, 1943 to 2009. J Occup Environ Med. 2019;61(11):887-897. doi:10.1097/JOM.0000000000001688	2019	X				
Zhang XY, Elfarra AA. Potential roles of myeloperoxidase and hypochlorous acid in metabolism and toxicity of alkene hydrocarbons and drug molecules containing olefinic moieties. Expert Opin Drug Metab Toxicol. 2017;13(5):513-524. doi:10.1080/17425255.2017.1271413	2017				X	
Khanchi, A., Hebbern, C. A., Zhu, J., & Cakmak, S. (2015). Exposure to volatile organic compounds and associated health risks in windsor, Canada. Atmospheric Environment, 120, 152-159.	2015	X				
Liu N, Li B, Cheng J, Zheng G, Li Y, Guan W. Wei Sheng Yan Jiu. 2015;44(2):190-195.	2015		X			
Redstone, S., Ahern, D., Scott, P., Le, P., & Millard, J. (2015). Mechanisms of cytotoxicity for bifunctional epoxide alkylating agents. The FASEB Journal, 29(1_supplement), 710-8.	2015		X	X	X	
Sathiakumar N, Brill I, Leader M, Delzell E. 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers--Preliminary exposure-response analyses. Chem Biol Interact. 2015;241:40-49. doi:10.1016/j.cbi.2015.09.003	2015	X				
Xiang M, Sun L, Dong X, et al. Association between Genetic Polymorphisms of DNA Repair Genes and Chromosomal Damage for 1,3-Butadiene-Exposed Workers in a Matched Study in China. Biomed Res Int. 2015;2015:234675. doi:10.1155/2015/234675	2015		X			
Yan Y, Peng L, Cheng N, Bai H, Mu L. Health risk assessment of toxic VOCs species for the coal fire well drillers. Environ Sci Pollut Res Int. 2015;22(19):15132-15144. doi:10.1007/s11356-015-4729-7	2015	X				
Cheng X, Zhang T, Zhao J, et al. The association between genetic damage in peripheral blood lymphocytes and polymorphisms of three glutathione S-transferases in Chinese workers exposed to 1,3-butadiene. Mutat Res. 2013;750(1-2):139-146. doi:10.1016/j.mrgentox.2012.10.008	2013		X	X		
Liu N, Wang X, Meng H, et al. Wei Sheng Yan Jiu. 2013;42(5):754-757.	2013		X			
Sangaraju D, Villalta P, Goggin M, Agunsoye MO, Campbell C, Tretyakova N. Capillary HPLC-accurate mass MS/MS quantitation of N7-(2,3,4-trihydroxybut-1-yl)-guanine adducts of 1,3-butadiene in human leukocyte DNA. Chem Res Toxicol. 2013;26(10):1486-1497. doi:10.1021/tx400213m	2013		X		X	
Sielken RL Jr, Valdez-Flores C. Quantitative risk assessment of exposures to butadiene in EU occupational settings based on the University of Alabama at Birmingham epidemiological study. Regul Toxicol Pharmacol. 2013;65(2):214-225. doi:10.1016/j.yrtph.2012.12.003	2013	X				
Boysen G, Georgieva NI, Bordeerat NK, et al. Formation of 1,2:3,4-diepoxybutane-specific hemoglobin adducts in 1,3-butadiene exposed workers. Toxicol Sci. 2012;125(1):30-40. doi:10.1093/toxsci/kfr272	2012				X	

Human Studies: Epidemiological and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
IRIS. 2012. 1,3-Butadiene. Washington, DC: Integrated Risk Information System. http://www.epa.gov/iris/subst/index.html. September 5, 2012.	2012	X				
Xiang M, Ao L, Yang H, et al. Chromosomal damage and polymorphisms of metabolic genes among 1, 3-butadiene-exposed workers in a matched study in China. Mutagenesis. 2012;27(4):415-421. doi:10.1093/mutage/ger091	2012		X		X	
Cave M, Falkner KC, Henry L, Costello B, Gregory B, McClain CJ. Serum cytokeratin 18 and cytokine elevations suggest a high prevalence of occupational liver disease in highly exposed elastomer/polymer workers. *J Occup Environ Med* . 2011;53(10):1128-1133. doi:10.1097/JOM.0b013e31822cfd68	2011			X		Hepatotoxicity
Sielken RL Jr, Valdez-Flores C. Butadiene cancer exposure-response modeling: based on workers in the styrene-butadiene-rubber industry: total leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia. Regul Toxicol Pharmacol. 2011;60(3):332-341. doi:10.1016/j.yrtph.2011.05.001	2011	X				
Georgieva, NL, G Boysen, Bordeerat N, Walker VE and Swenberg JA. (2010). Exposure-response of 1,2:3,4-diepoxybutane-specific N-terminal valine adducts in mice and rats after inhalation exposure to 1,3-butadiene.Toxicol Sci,115, 322-329.	2010				X	
Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L and Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. (2009). A review of human carcinogens--Part F: chemical agents and related occupations. Lancet Oncol. 10 (12),1143-4.	2009	X				
Wickliffe JK, Ammenheuser MM, Adler PJ, et al. 2009. Evaluation of frequencies of HPRT mutant lymphocytes in butadiene polymer workers in a southeast Texas facility. Environ Mol Mutagen 50(2):82-87.	2009		X			
International Agency for Research on Cancer (IARC). (2008). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 97. 1,3-Butadiene, ethylene oxide, and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). Lyon: International Agency for Research on Cancer. pp. 45-185.	2008	X				
Liu S, Ao L, Du B, et al. 2008. HPRT mutations in lymphocytes from 1,3-butadiene-exposed workers in China. Environ Health Perspect 116:203-208.	2008		X			
Albertini RJ, Sram RJ, Vacek PM, et al. 2007. Molecular epidemiological studies in 1,3-butadiene exposed Czech workers: Female-male comparisons. Chem Biol Interact 166(1-3):63-77.	2007		X		X	
Cheng H, Sathiakumar N, Graff J, et al. 2007. 1,3-Butadiene and leukemia among synthetic rubber industry workers: Exposure-response relationships. Chem Biol Interact 166(1-3):15-24.	2007	X				
Sathiakumar N, Delzell., Cheng H, Lynch J, Sparks W and Macaluso M. (2007). Validation of 1,3-butadiene exposure estimates for workers at a synthetic rubber plant, Chem. -Biol. Interact. 166, 29–43.	2007	X				
Swenberg JA, Boysen G, Georgieva N, Bird MG, Lewis RJ. (2007). Future directions in butadiene risk assessment and the role of cross-species internal dosimetry. Chem Biol Interact. 166: 78-83.	2007				X	
Khalil, M, M Abudiab, and AE Ahmed. 2007. Clinical evaluation of 1,3-butadiene neurotoxicity in humans. Tox Ind Health 23: 141-6.	2007					Neurological risk
HEI. 2006. An updated study of mortality among North American synthetic rubber industry workers. Number 132. Boston, MA: Health Effects Institute.	2006	X				

Human Studies: Epidemiological and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
Knox EG. 2006. Roads, railways, and childhood cancers. J Epidemiol Community Health 60(2):136-141.	2006	X				
Lovreglio P, Bukvic N, Fustinoni S, et al. 2006. Lack of genotoxic effect in workers exposed to very low doses of 1,3-butadiene. Arch Toxicol 80(6):378-381.	2006		X			
Abdel-Rahman SZ, Ammenheuser MM, Omiecinski CJ, et al. 2005. Variability in human sensitivity to 1,3-butadiene: Influence of polymorphisms in the 5'-flanking region of the microsomal epoxide hydrolase gene (EPHX1). Toxicol Sci 85(1):624-631.	2005		X			
Graff JJ, Sathlakumar N, Macaluso M, et al. 2005. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. J Occup Med 47:916-932.	2005	X				
Knox EG. 2005. Childhood cancers and atmospheric carcinogens. J Epidemiol Community Health 59:101-105.	2005	X				
Sathiakumar N, Graff J, Macaluso M, et al. 2005. An updated study of mortality among North American synthetic rubber industry workers. Occup Environ Med 62:822-829.	2005	X				
Tsai SP, Ahmed FS, Ransdell JD, et al. 2005. A hematology surveillance study of petrochemical workers exposed to 1,3 butadiene. J Occup Environ Hyg 2(10):508-515.	2005					Hematoxicity
Albertini R (2004). Mechanistic insights from biomarker studies: somatic mutations and rodent/human comparisons following exposures to potential carcinogens, in: R. J. Buffler P, Bann R, Bird M, Bofetta P (Ed.), Mechanisms Epidemiology, IARC Sci Publ, pp. 33-40.	2004				X	
Fustinoni S, Perbellini L, Soleo L, et al. 2004. Biological monitoring in occupational exposure to low levels of 1,3-butadiene. Toxicol Lett 149(1-3):353-360.	2004		X			
Macaluso M, Larson R, Lynch J, et al. 2004. Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber workers. J Occup Environ Hyg 1(6):371-390.	2004	X				
Macaluso, M, Larson, R, Lynch, J, Lipton, S and Delzell, E. (2004). Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber workers. J. Occup. Environ. Hyg. 1, 371-390.	2004	X				
Abdel-Rahman SZ, El-Zein RA, Ammenheuser MM, et al. 2003. Variability in human sensitivity to 1,3-butadiene: Influence of the allelic variants of the microsomal epoxide hydrolase gene. Environ Mol Mutagen 41(2):140-146.	2003		X			
HEI. 2003. Biomarkers in Czech workers exposed to 1,3-butadiene: A transitional epidemiologic study. Number 116. Boston, MA: Health Effects Institute.	2003		X			
Nagata, Y. 2003. Measurement of odor threshold by triangular odor bag method. Odor Measurement Review, Japan Ministry of the Environment. pp. 118-127.	2003					Acute
EU RAR (2002). European Union Risk Assessment Report for 1,3-butadiene. Vol. 20. European Chemicals Bureau (http: //ecb. jrc. ec. europa. eu/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/butadienereport019. pdf)	2002	X			X	Eye irritation
Lin YS, Smith TJ, Wypij D, et al. 2002. Association of the blood/air partition coefficient of 1,3-butadiene with blood lipids and albumin. Environ Health Perspect 110(2):165-168.	2002				X	
Abdel-Rahman SZ, Ammenheuser MM, Ward JB. 2001. Human sensitivity to 1,3-butadiene: Role of microsomal epoxide hydrolase polymorphisms. Carcinogenesis 22(3):415-423.	2001		X			
Albertini RJ, Sram RJ, Vacek PM, et al. 2001. Biomarkers for assessing occupational exposures to 1,3-butadiene. Chem Biol Interact 135-136:429-453.	2001		X			

Human Studies: Epidemiological and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
Ammenheuser MM, Bechtold WE, Abdel-Rahman SZ, et al. 2001. Assessment of 1,3-butadiene exposure in polymer production workers using HPRT mutations in lymphocytes as a biomarker. Environ Health Perspect 109(12):1249-1255.	2001		X			
Bergemann, P, Sram RJ and Neumann HG. (2001). Hemoglobin adducts of epoxybutene in workers occupationally exposed to 1,3-butadiene. Arch Toxicol 74: 680-87.	2001				X	
Delzell E, Macaluso M, Sathiakumar NandMatthews R. (2001). Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. Chem Biol Interact, 135-136, 515-34.	2001	X				
Delzell et al 2006	2001	X				
Divine BJ, Hartman CM. 2001. A cohort mortality study among workers at a 1,3 butadiene facility. Chem Biol Interact 135-136:535-553.	2001	X				Cardiovascular effects
Hayes RB, Zhang L, Swenberg JA, et al. 2001. Markers for carcinogenicity among butadiene-polymer workers in China. Chem Biol Interact 135-136:455-464.	2001		X			
Lin YS, Smith TJ, Kelsey KT, et al. 2001. Human physiologic factors in respiratory uptake of 1,3-butadiene. Environ Health Perspect 109(9):921-926.	2001				X	
Smith TJ, Lin YS, Mezzetti M, et al. 2001. Genetic and dietary factors affecting human metabolism of 1,3-butadiene. Chem Biol Interact 135-136:407-428.	2001				X	
Ward JB, Abdel-Rahman SZ, Henderson RF, et al. 2001. Assessment of butadiene exposure in synthetic rubber manufacturing workers in Texas using frequencies of hprt mutant lymphocytes as a biomarker. Chem Biol Interact 135-136:465-483.	2001		X			
Zhao C, Vodicka P, Sram RJ, et al. 2001. DNA adducts of 1,3-butadiene in humans: Relationships to exposure, GST genotypes, single-strand breaks, and cytogenetic end points. Environ Mol Mutagen 37(3):226-230.	2001		X			
Hayes RB, Zhang L, Yin S, et al. 2000. Genotoxic markers among butadiene polymer workers in China. Carcinogenesis 21(1):55-62.	2000		X			
Ma H, Wood TG, Ammenheuser MM, et al. 2000. Molecular analysis of hprt mutant lymphocytes from 1,3-butadiene-exposed workers. Environ Mol Mutagen 36(1):59-71.	2000		X			
Zhao, C, P Vodicka, RJ Sram, and K Hemminki. 2001. DNA adducts of 1,3-butadiene in humans: relationships to exposure, GST genotypes, single-strand breaks, and cytogenetic end points. Environ Mol Mutagen 37: 226-30.	2000		X			
Irons RD, Pyatt DW. 1998. Dithiocarbamates as potential confounders in butadiene epidemiology. Carcinogenesis 19(4):539-542.	1998	X				
Šrám RJ, Rossner P, Peltonen K, et al. 1998. Chromosomal aberrations, sister-chromatid exchanges, cells with high frequency of SCE, micronuclei and comet assay parameters in 1,3-butadiene-exposed workers. Mutat Res 419(1-3):145-154.	1998		X			
Hallberg LM, Bechtold WE, Grady J, et al. 1997. Abnormal DNA repair activities in lymphocytes of workers exposed to 1,3-butadiene. Mutat Res 383(3):213-221.	1997		X			
Delzell, E, N Sathiakumar, and M Hovinga. (1996). A follow-up study of synthetic rubber workers. Toxicology 113, 182-189.	1996	X				
Divine BJ, Hartman CM. 1996. Mortality update of butadiene production workers. Toxicology 113(1-3):169-181.	1996	X				Cardiovascular effects

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Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
Hayes RB, Xi L, Bechtold WE, et al. 1996. hprt Mutation frequency among workers exposed to 1,3-butadiene in China. Toxicology 113(1-3):100-105.	1996		X			
Macaluso, M, Larson, R, Delzell, E, Sathiakumar, N, Hovinga, M, Julian, J, Muir, D and Cole, P. (1996) Leukemia and cumulative exposure to butadiene, styrene and benzene among workers in the synthetic rubber industry. Toxicology, 113, 190-202.	1996	X				
Sorsa M, Osterman-Golkar S, Peltonen K, et al. 1996. Assessment of exposure to butadiene in the process industry [Abstract]. Toxicology 113(1-3):77-83.	1996		X			
Tates AD, van Dam FJ, de Zwart FA, et al. 1996. Biological effect monitoring in industrial workers from the Czech Republic exposed to low levels of butadiene [Abstract]. Toxicology 113(1-3):91-99.	1996		X			
Ward JB, Ammenheuser MM, Whorton EB, et al. 1996. Biological monitoring for mutagenic effects of occupational exposure to butadiene. Toxicology 110:1-7.	1996		X			
Au WW, Bechtold WE, Whorton EB, et al. 1995. Chromosome aberrations and response to γ-ray challenge in lymphocytes of workers exposed to 1,3-butadiene. Mutat Res 334:125-130.	1995		X			
Delzell, E, N Sathiakumar, and M Macaluso. (1995). A follow-up study of synthetic rubber workers. Final report prepared under contract to International Institute of Synthetic Rubber Producers.	1995	X				
Kelsey KT, Wiencke JK, Ward J, et al. 1995. Sister-chromatid exchanges, glutathione S-transferase θ deletion and cytogenetic sensitivity to diepoxybutane in lymphocytes from butadiene monomer production workers. Mutat Res 335(3):267-273.	1995		X			
Ward EM, Fajen JM, Ruder AM, et al. 1995. Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. Environ Health Perspect 103(6):598-603	1995	X				Cardiovascular effects
Cowles SR, Tsai SP, Snyder PJ, et al. 1994. Mortality, morbidity, and haematological results from a cohort of long-term workers involved in 1,3-butadiene monomer production. Occup Environ Med 51(5):323-329.	1994	X				
Sorsa et al. 1994	1994		X			
Ward JB, Ammenheuser MM, Bechtold WE, et al. 1994. hprt Mutant lymphocyte frequencies in workers at a 1,3-butadiene production plant. Environ Health Perspect 102(Suppl 9):79-85.	1994		X			
Divine BJ, Wendt JK, Hartman CM. 1993. Cancer mortality among workers at a butadiene production facility. In: Sorsa M, Peltonen K, Vainio H, et al., eds. Butadiene and styrene: Assessment of healh hazards. IARC Scientific Publications No. 127. Lyon, France: International Agency for Research on Cancer, 345-362.	1993	X				
Weincke, JK and KT Kelsey. 1993. Susceptibility to induction of chromosomal damage by metabolites of 1,3-butadiene and its relationship to 'spontaneous' sister chromatid exchange frequencies in human lymphocytes. In Butadiene and styrene: assessment of health hazards, IARC Scientific Publications Vol. 127. (Sorsa, M., Peltonen, K., Vainio, H., et al., eds.). Lyon, France: International Agency for Research on Cancer, pp. 265-273.	1993		X			
Santos-Burgoa C, Matanoski GM, Zeger S, et al. 1992. Lymphohematopoietic cancer in styrene-butadiene polymerization workers. Am J Epidemiol 136(7):843-854.	1992	X				

Human Studies: Epidemiological and *in vitro*

Citation	Year	Carcinogenicity	Genotoxicity	Mechanistic	ADME	Other
Divine BJ. 1990. An update on mortality among workers at a 1,3-butadiene facility — preliminary results. Environ Health Perspect 86:119-128.	1990	X				
Matanoski GM, Santos-Burgoa C, Schwartz L. 1990. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). Environ Health Perspect 86:107-117.	1990	X				Cardiovascular effects
Matanoski GM, Santos-Burgoa C, Zeger SL, et al. 1989b. Nested case-control study of lymphopoietic cancers in workers in the styrene-butadiene polymer manufacturing industry (final report prepared under contract to International Institute of Synthetic Rubber Producers, Inc.). Baltimore, MD: The Johns Hopkins University, School of Hygiene and Public Health.	1989	X				
Matanoski GM, Santos-Burgoa C, Schwartz L. 1988. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry 1943-1982 (final report prepared under contract to International Institute of Synthetic Rubber Producers, Inc.). Baltimore, MD: The Johns Hopkins University, School of Hygiene and Public Health.	1988	X				Cardiovascular effects
Downs TD, Crane MM, Kim KW. 1987. Mortality among workers at a butadiene facility. Am J Ind Med 12:311-329.	1987	X				
Matanoski GM, Schwartz L. 1987. Mortality of workers in styrene-butadiene polymer production. J Occup Med 29(8):675-680.	1987	X				Cardiovascular effects
Ruth, JH. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am Ind Hyg J 47:A142-A151.	1986					Acute
Checkoway H, Williams TM. 1982. A hematology survey of workers at a styrene-butadiene synthetic rubber manufacturing plant. Am Ind Hyg Assoc J 43:164-169.	1982					Hematoxicity
McMichael AJ, Spirtas R, Kupper LL. 1974. An epidemiologic study of mortality within a cohort of rubber workers, 1964-1972. J Occup Med 16:458-464.	1974					Cardiovascular effects
Carpenter CP, Shaffer CB, Weir CS, Smyth HF. 1944. Studies on the inhalation of 1,3-butadiene; with a comparison of its narcotic effect with benzol, toluol and styrene, and a note on the elimination of styrene by the human. J Ind Hyg Toxicol 26; 69-78	1944					Hematoxicity, eye irritation
Wilson RH. 1944. Health hazards encountered in the manufacture of synthetic rubber. J Am Med Assoc 124(11):701-703.	1944					Eye irritation
Larion ov, LF, TA Shtessel', and EI Nusel'man. 1934. The physiological action of butadiene, butene-2 and isoprene. Kazanskii Meditsinkii Zhurnal 30:440-45 (HSE translation no. 10855).	1934					Acute

Non-occupational Exposure Studies				
Author	Year	Consumer	Indoor environment	General population biomonitoring
Al-Awadi L. Assessment of indoor levels of volatile organic compounds and carbon dioxide in schools in Kuwait. J Air Waste Manag Assoc. 2018;68(1):54-72. doi:10.1080/10962247.2017.1365781	2018		X	
Aquilina NJ, Delgado-Saborit JM, Meddings C, Baker S, Harrison RM, Jacob P, et al. Environmental and biological monitoring of exposures to PAHs and ETS in the general population. Environ Int 2010;36(7):763-771.	2010		X	
Boyle EB, Viet SM, Wright DJ, et al. Assessment of Exposure to VOCs among Pregnant Women in the National Children's Study. Int J Environ Res Public Health. 2016;13(4):376. Published 2016 Mar 29. doi:10.3390/ijerph13040376	2016			X
Carteret M, Pauwels JF, Hanoune B. Emission factors of gaseous pollutants from recent kerosene space heaters and fuels available in France in 2010. Indoor Air. 2012;22(4):299-308. doi:10.1111/j.1600-0668.2011.00763.x	2012	X	X	
Chan WC, Lee SC, Chen YM, Mak B, Wong KV, Chan CS, et al. Indoor air quality in new hotels' guest rooms of the major world factory region. Int J Hosp Manag 2009;28(1):26-32.	2009		X	

Non-occupational Exposure Studies				
Author	Year	Consumer	Indoor environment	General population biomonitoring
Chong NS, Abdulramoni S, Patterson D, Brown H. Releases of Fire-Derived Contaminants from Polymer Pipes Made of Polyvinyl Chloride. Toxics. 2019;7(4):57. Published 2019 Nov 11. doi:10.3390/toxics7040057	2019	X		
Delgado-Saborit JM, Aquilina NJ, Meddings C, Baker S, Harrison RM. Relationship of personal exposure to volatile organic compounds to home, work and fixed site outdoor concentrations. Sci Total Environ 2011;409(3):478-488.	2011	X	X	
Eckert E, Schmid K, Schaller B, Hiddemann-Koca K, Drexler H, Göen T. Mercapturic acids as metabolites of alkylating substances in urine samples of German inhabitants [published correction appears in Int J Hyg Environ Health. 2011 Sep;214(5):413]. Int J Hyg Environ Health.	2011			X
Gustafson P, Barregard L, Strandberg B, Sallsten G. The impact of domestic wood burning on personal, indoor and outdoor levels of 1,3-butadiene, benzene, formaldehyde and acetaldehyde. J Environ Monit 2007;9(1):23-32.	2007		X	
Hagenbjörk-Gustafsson A, Tornevi A, Andersson EM, et al. Determinants of personal exposure to some carcinogenic substances and nitrogen dioxide among the general population in five Swedish cities. J Expo Sci Environ Epidemiol. 2014;24(4):437-443. doi:10.1038/jes.2013.57	2014		X	

Non-occupational Exposure Studies				
Author	Year	Consumer	Indoor environment	General population biomonitoring
Heavner DL, Morgan WT, Ogden MW. Determination of volatile organic compounds and respirable suspended particulate matter in New Jersey and Pennsylvania homes and workplaces. Environ Int 1996;22(2):159-183.	1996		X	
Huang Y, Su T, Wang L, et al. Evaluation and characterization of volatile air toxics indoors in a heavy polluted city of northwestern China in wintertime. Sci Total Environ. 2019;662:470-480. doi:10.1016/j.scitotenv.2019.01.250	2019		X	
Huy LN, Lee SC, Zhang Z. Human cancer risk estimation for 1,3-butadiene: An assessment of personal exposure and different microenvironments. Sci Total Environ. 2018;616-617:1599-1611. doi:10.1016/j.scitotenv.2017.10.152	2018		X	
Khanchi, A., Hebbern, C. A., Zhu, J., & Cakmak, S. (2015). Exposure to volatile organic compounds and associated health risks in windsor, Canada. Atmospheric Environment, 120, 152-159.	2015		X	
Kim YM, Harrad S, Harrison R. Concentrations and sources of volatile organic compounds in urban domestic and public microenvironments. Indoor Built Environ 2001;10(3-4):147-153.	2001		X	

Non-occupational Exposure Studies				
Author	Year	Consumer	Indoor environment	General population biomonitoring
Kim YM, Harrad S, Harrison RM. Levels and sources of personal inhalation exposure to volatile organic compounds. Environ Sci Technol 2002;36(24):5405-5410.	2002	X	X	
Kinney PL, Chillrud SN, Ramstrom S, Ross J, Spengler JD. Exposures to multiple air toxics in New York City. Environ Health Perspect 2002;110:539-546.	2002		X	
Kotapati S, Matter BA, Grant AL, Tretyakova NY. Quantitative analysis of trihydroxybutyl mercapturic acid, a urinary metabolite of 1,3-butadiene, in humans. Chem Res Toxicol. 2011;24(9):1516-1526. doi:10.1021/tx2001306	2011			X
Logue JM, Mckone TE, Sherman MH, Singer BC. Hazard assessment of chemical air contaminants measured in residences. Indoor Air 2011;21(2):92-109.	2011		X	
Logue JM, McKone TE, Sherman MH, Singer BC. Hazard assessment of chemical air contaminants measured in residences. Indoor Air. 2011;21(2):92-109. doi:10.1111/j.1600-0668.2010.00683.x	2011		X	
Raj AT, Patil S, Sarode SC, Sarode GS, Rajkumar C. Evaluating the association between household air pollution and oral cancer. Oral Oncol. 2017;75:178-179. doi:10.1016/j.oraloncology.2017.11.012	2017		X	

Non-occupational Exposure Studies				
Author	Year	Consumer	Indoor environment	General population biomonitoring
Serrano-Trespalacios PI, Ryan L, Spengler JD. Ambient, indoor and personal exposure relationships of volatile organic compounds in Mexico City Metropolitan Area. J Exposure Anal Environ Epidemiol 2004;14:S118-S132.	2004		X	
Sjöström M, Julander A, Strandberg B, Lewné M, Bigert C. Airborne and Dermal Exposure to Polycyclic Aromatic Hydrocarbons, Volatile Organic Compounds, and Particles among Firefighters and Police Investigators. Ann Work Expo Health. 2019;63(5):533-545. doi:10.1093/annweh/wxz030	2019		X	
Weisel CP, Alimokhtari S, Sanders PF. Indoor air VOC concentrations in suburban and rural New Jersey. Environ Sci Technol 2008;42(22):8231-8238.	2008		X	
Yazar, M., Bellander, T., & Merritt, A. S. (2011). Personal exposure to carcinogenic and toxic air pollutants in Stockholm, Sweden: A comparison over time. Atmospheric environment, 45(17), 2999-3004.	2011		X	
Zhou J, You Y, Bai Z, Hu Y, Zhang J, Zhang N. Health risk assessment of personal inhalation exposure to volatile organic compounds in Tianjin, China. Sci Total Environ. 2011;409(3):452-459. doi:10.1016/j.scitotenv.2010.10.022	2011		X	

Occupational Exposure Studies					
Author	Year	Manufacturing	Processing	Disposal / waste	Other / Notes
Sjöström M, Julander A, Strandberg B, Lewné M, Bigert C. Airborne and Dermal Exposure to Polycyclic Aromatic Hydrocarbons, Volatile Organic Compounds, and Particles among Firefighters and Police Investigators. Ann Work Expo Health. 2019;63(5):533-545.	2019				Fire
Vallecillos, L., Sanmartin, J., Marcé, R. M., & Borrull, F. (2019). Determination of 1, 3-butadiene degradation products in air samples by thermal desorption-gas chromatography-mass spectrometry. Atmospheric environment, 196, 95-102.	2019	X			
Almerud P, Akerstrom M, Andersson EM, Strandberg B, Sallsten G. Low personal exposure to benzene and 1,3-butadiene in the Swedish petroleum refinery industry. Int Arch Occup Environ Health. 2017;90(7):713-724. doi:10.1007/s00420-017-1234-y	2017		X		
Sangaraju D, Boldry EJ, Patel YM, et al. Isotope Dilution nanoLC/ESI+-HRMS3 Quantitation of Urinary N7-(1-Hydroxy-3-buten-2-yl) Guanine Adducts in Humans and Their Use as Biomarkers of Exposure to 1,3-Butadiene. Chem Res Toxicol. 2017;30(2):678-688. doi:10.1021/acs.chemrestox.6b00407	2017				Unclear

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Loser, E., & Tordoir, W. F. (1996). Evaluation of butadiene and isoprene health risks Proceedings of the International Symposium held in Blaine, Washington on June 27-29, 1995-Foreword.	1996
Melnick, R. L., Huff, J. E., Bird, M. G., & Acquavella, J. F. (1990). Symposium overview: toxicology, carcinogenesis, and human health aspects of 1, 3-butadiene.	1990

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Frigerio, G., Mercadante, R., Campo, L., Polledri, E., Boniardi, L., Olgiati, L., Missineo, P., Fustinoni, S.	Urinary biomonitoring of subjects with different smoking habits. Part I: Profiling mercapturic acids.	Toxicology letters	2020	
Biren, C., Zhang, L., Bhandari, D., Blount, BC., De Jesús, VR.	Isoprene Exposure in the United States Based on Urinary IPM3: NHANES 2015-2016.	Environmental science & technology	2020	
Etemadi, A., Poustchi, H., Calafat, AM., Blount, BC., De Jesús, VR., Wang, L., Pourshams, A., Shakeri, R., Inoue-Choi, M., Shiels, MS., Roshandel, G., Murphy, G., Sosnoff, CS., Bhandari, D., Feng, J., Xia, B., Wang, Y., Meng, L., Kamangar, F., Brennan, P., Boffetta, P., Dawsey, SM., Abnet, CC., Malekzadeh, R., Freedman, ND.	Opiate and Tobacco Use and Exposure to Carcinogens and Toxicants in the Golestan Cohort Study.	Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology	2020	
Boldry, EJ., Yuan, JM., Carmella, SG., Wang, R., Tessier, K., Hatsukami, DK., Hecht, SS., Tretyakova, NY.	Effects of 2-Phenethyl Isothiocyanate on Metabolism of 1,3-Butadiene in Smokers.	Cancer prevention research (Philadelphia, Pa.)	2020	
Jokipii Krueger, CC., Madugundu, G., Degner, A., Patel, Y., Stram, DO., Church, TR., Tretyakova, N.	Urinary N7-(1-hydroxy-3-buten-2-yl) guanine adducts in humans: temporal stability and association with smoking.	Mutagenesis	2020	
St Helen, G., Liakoni, E., Nardone, N., Addo, N., Jacob, P., Benowitz, NL.	Comparison of Systemic Exposure to Toxic and/or Carcinogenic Volatile Organic Compounds (VOC) during Vaping, Smoking, and Abstention.	Cancer prevention research (Philadelphia, Pa.)	2020	
Oladipupo, OA., Dutta, D., Chong, NS.	Analysis of chemical constituents in mainstream bidi smoke.	BMC chemistry	2019	
Kocher, GJ., Sesia, SB., Lopez-Hilfiker, F., Schmid, RA.	Surgical smoke: still an underestimated health hazard in the operating theatre.	European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery	2019	Smoke generated from electrocautery dissection
Murphy, SE., Park, SL., Balbo, S., Haiman, CA., Hatsukami, DK., Patel, Y., Peterson, LA., Stepanov, I., Stram, DO., Tretyakova, N., Hecht, SS., Le Marchand, L.	Tobacco biomarkers and genetic/epigenetic analysis to investigate ethnic/racial differences in lung cancer risk among smokers.	NPJ precision oncology	2018	
Lorkiewicz, P., Riggs, DW., Keith, RJ., Conklin, DJ., Xie, Z., Sutaria, S., Lynch, B., Srivastava, S., Bhatnagar, A.	Comparison of Urinary Biomarkers of Exposure in Humans Using Electronic Cigarettes, Combustible Cigarettes, and Smokeless Tobacco.	Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco	2019	
Boldry, EJ., Patel, YM., Kotapati, S., Esades, A., Park, SL., Tiirikainen, M., Stram, DO., Le Marchand, L., Tretyakova, N.	Genetic Determinants of 1,3-Butadiene Metabolism and Detoxification in Three Populations of Smokers with Different Risks of Lung Cancer.	Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology	2017	
Shahab, L., Goniewicz, ML., Blount, BC., Brown, J., McNeill, A., Alwis, KU., Feng, J., Wang, L., West, R.	Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study.	Annals of internal medicine	2017	
Goniewicz, ML., Gawron, M., Smith, DM., Peng, M., Jacob, P., Benowitz, NL.	Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study.	Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco	2017	
Mitova, MI., Campelos, PB., Goujon-Ginglinger, CG., Maeder, S., Mottier, N., Rouget, EG., Tharin, M., Tricker, AR.	Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality.	Regulatory toxicology and pharmacology : RTP	2016	

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Jain, RB.	Distributions of selected urinary metabolites of volatile organic compounds by age, gender, race/ethnicity, and smoking status in a representative sample of U.S. adults.	Environmental toxicology and pharmacology	2015	
Jain, RB.	Levels of selected urinary metabolites of volatile organic compounds among children aged 6-11 years.	Environmental research	2015	
Varlet, V., Farsalinos, K., Augsburger, M., Thomas, A., Etter, JF.	Toxicity assessment of refill liquids for electronic cigarettes.	International journal of environmental research and public health	2015	
St Helen, G., Jacob, P., Peng, M., Dempsey, DA., Hammond, SK., Benowitz, NL.	Intake of toxic and carcinogenic volatile organic compounds from secondhand smoke in motor vehicles.	Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology	2014	
Park, SL., Kotapati, S., Wilkens, LR., Tiirikainen, M., Murphy, SE., Tretyakova, N., Le Marchand, L.	1,3-Butadiene exposure and metabolism among Japanese American, Native Hawaiian, and White smokers.	Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology	2014	
Sleiman, M., Logue, JM., Luo, W., Pankow, JF., Gundel, LA., Destaillats, H.	Inhalable constituents of thirdhand tobacco smoke: chemical characterization and health impact considerations.	Environmental science & technology	2014	
Ashley, M., Dixon, M., Prasad, K.	Relationship between cigarette format and mouth-level exposure to tar and nicotine in smokers of Russian king-size cigarettes.	Regulatory toxicology and pharmacology : RTP	2014	
Zhang, X., Xiong, W., Shi, L., Hou, H., Hu, Q.	Simultaneous determination of five mercapturic acid derived from volatile organic compounds in human urine by LC-MS/MS and its application to relationship study.	Journal of chromatography. B, Analytical technologies in the biomedical and life sciences	2014	
Sampson, MM., Chambers, DM., Pazo, DY., Moliere, F., Blount, BC., Watson, CH.	Simultaneous analysis of 22 volatile organic compounds in cigarette smoke using gas sampling bags for high-throughput solid-phase microextraction.	Analytical chemistry	2014	
Sakaguchi, C., Kakehi, A., Minami, N., Kikuchi, A., Futamura, Y.	Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting.	Regulatory toxicology and pharmacology : RTP	2014	
Pan, Y., Hu, Y., Wang, J., Ye, L., Liu, C., Zhu, Z.	Online characterization of isomeric/isobaric components in the gas phase of mainstream cigarette smoke by tunable synchrotron radiation vacuum ultraviolet photoionization time-of-flight mass spectrometry and photoionization efficiency curve simulation.	Analytical chemistry	2013	
Hyodo, T., Minagawa, K., Inoue, T., Fujimoto, J., Minami, N., Bito, R., Mikita, A.	Estimation of mouth level exposure to smoke constituents of cigarettes with different tar levels using filter analysis.	Regulatory toxicology and pharmacology : RTP	2013	
Soeteman-Hernández, LG., Bos, PM., Talhout, R.	Tobacco smoke-related health effects induced by 1,3-butadiene and strategies for risk reduction.	Toxicological sciences : an official journal of the Society of Toxicology	2013	

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Dewangan, S., Chakrabarty, R., Zielinska, B., Pervez, S.	Emission of volatile organic compounds from religious and ritual activities in India.	Environmental monitoring and assessment	2013	Smoke from incense burning
Shepperd, CJ., Eldridge, A., Camacho, OM., McAdam, K., Proctor, CJ., Meyer, I.	Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes.	Regulatory toxicology and pharmacology : RTP	2013	
Jacob, P., Abu Raddaha, AH., Dempsey, D., Havel, C., Peng, M., Yu, L., Benowitz, NL.	Comparison of nicotine and carcinogen exposure with water pipe and cigarette smoking.	Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology	2013	
Yuan, JM., Gao, YT., Wang, R., Chen, M., Carmella, SG., Hecht, SS.	Urinary levels of volatile organic carcinogen and toxicant biomarkers in relation to lung cancer development in smokers.	Carcinogenesis	2012	
Gordon, SM., Brinkman, MC., Meng, RQ., Anderson, GM., Chuang, JC., Kroeger, RR., Reyes, IL., Clark, PI.	Effect of cigarette menthol content on mainstream smoke emissions.	Chemical research in toxicology	2011	
Chowdhury, KK., Meftahuzzaman, SM., Rickta, D., Chowdhury, TK., Chowdhury, BB., Ireen, ST.	Electrosurgical smoke: a real concern.	Mymensingh medical journal : MMJ	2011	Electrosurgical smoke
Cunningham, FH., Fiebelkorn, S., Johnson, M., Meredith, C.	A novel application of the Margin of Exposure approach: segregation of tobacco smoke toxicants.	Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association	2011	
Lindner, D., Smith, S., Leroy, CM., Tricker, AR.	Comparison of exposure to selected cigarette smoke constituents in adult smokers and nonsmokers in a European, multicenter, observational study.	Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology	2011	
Wang, J., Liang, Q., Mendes, P., Sarkar, M.	Is 24h nicotine equivalents a surrogate for smoke exposure based on its relationship with other biomarkers of exposure?	Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals	2011	
Papaefstathiou, E.,Bezantakos, S.,Stylianou, M.,Biskos, G.,Agapiou, A.	Comparison of particle size distributions and volatile organic compounds exhaled by e-cigarette and cigarette users	Journal of Aerosol Science	2020	
Belushkin, M.,Tafin Djoko, D.,Esposito, M.,Korneliou, A.,Jeannet, C.,Lazzerini, M.,Jaccard, G.	Selected Harmful and Potentially Harmful Constituents Levels in Commercial e-Cigarettes	Chemical Research in Toxicology	2020	
Uchiyama, S.,Noguchi, M.,Sato, A.,Ishitsuka, M.,Inaba, Y.,Kunugita, N.	Determination of Thermal Decomposition Products Generated from E-Cigarettes	Chemical Research in Toxicology	2020	
Keith, R. J.,Fetterman, J. L.,Orimoloye, O. A.,Dardari, Z.,Lorkiewicz, P. K.,Hamburg, N. M.,Defilippis, A. P.,Blaha, M. J.,Bhatnagar, A.	Characterization of Volatile Organic Compound Metabolites in Cigarette Smokers, Electronic Nicotine Device Users, Dual Users, and Nonusers of Tobacco	Nicotine and Tobacco Research	2020	
Stroud, L.,Werner, E.,Matteson, K.,Carey, M.,Helen, G. S.,Eissenberg, T.,Scott-Sheldon, L. A. J.	Waterpipe (hookah) tobacco use in pregnancy: use, preferences and perceptions of flavours	Tobacco control	2020	
Helen, G. S.,Liakoni, E.,Nardone, N.,Addo, N.,Jacob, P.,Benowitz, N. L.	Comparison of systemic exposure to toxic and/or carcinogenic Volatile Organic Compounds (VOC) during vaping, smoking, and abstention	Cancer Prevention Research	2020	
Giotopoulou, G. A.,Stathopoulos, G. T.	Effects of Inhaled Tobacco Smoke on the Pulmonary Tumor Microenvironment		2020	

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Eldridge, A.,Betson, T.,Gama, M. V.,Errington, G.,McAdam, K.	Investigation of number of replicate measurements required to meet cigarette smoke chemistry regulatory requirements measured under Canadian intense smoking conditions	Regulatory Toxicology and Pharmacology	2019	
Goniewicz, M.	ES11.06 Toxicology of Tobacco and Metabolites, and Impact on Cancer	Journal of Thoracic Oncology	2019	
Pack, E. C.,Kim, H. S.,Jang, D. Y.,Koo, Y. J.,Yu, H. H.,Lee, S. H.,Lim, K. M.,Choi, D. W.	Risk assessment of toxicants on WHO TobReg priority list in mainstream cigarette smoke using human-smoked yields of Korean smokers	Environmental Research	2019	
Digiacomo, S. I.,Jazayeri, M. A.,Barua, R. S.,Ambrose, J. A.	Environmental tobacco smoke and cardiovascular disease	International Journal of Environmental Research and Public Health	2019	
Ma, B.,Stepanov, I.,Hecht, S. S.	Recent studies on DNA adducts resulting from human exposure to tobacco smoke	Toxics	2019	
Goniewicz, M.	Just Water Vapor? Toxicology Perspectives on Electronic Cigarettes	Journal of Thoracic Oncology	2018	
Yuki, D.,Takeshige, Y.,Nakaya, K.,Futamura, Y.	Assessment of the exposure to harmful and potentially harmful constituents in healthy Japanese smokers using a novel tobacco vapor product compared with conventional cigarettes and smoking abstinence	Regulatory Toxicology and Pharmacology	2018	
McAdam, K.,Murphy, J.,Eldridge, A.,Meredith, C.,Proctor, C.	Integrating chemical, toxicological and clinical research to assess the potential of reducing health risks associated with cigarette smoking through reducing toxicant emissions	Regulatory Toxicology and Pharmacology	2018	
Mallock, N.,Böss, L.,Burk, R.,Danziger, M.,Welsch, T.,Hahn, H.,Trieu, H. L.,Hahn, J.,Pieper, E.,Henkler-Stephani, F.,Hutzler, C.,Luch, A.	Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks	Archives of Toxicology	2018	
Pickworth, W. B.,Rosenberry, Z. R.,Yi, D.,Pitts, E. N.,Lord-Adem, W.,Koszowski, B.	Cigarillo and Little Cigar Mainstream Smoke Constituents from Replicated Human Smoking	Chemical Research in Toxicology	2018	
Pack, E. C.,Jang, D. Y.,Kim, H. S.,Lee, S. H.,Kim, H. Y.,Song, S. H.,Cho, H. S.,Kwon, K. H.,Park, K. H.,Lim, K. M.,Choi, D. W.	Mixture risk assessment of selected mainstream cigarette smoke constituents generated from low-yield cigarettes in South Korean smokers	Regulatory Toxicology and Pharmacology	2018	
Keith, R. J.,Fetterman, J. L.,Riggs, D. W.,O'Toole, T.,Nystoriak, J. L.,Holbrook, M.,Lorkiewicz, P.,Bhatnagar, A.,Defilippis, A. P.,Hamburg, N. M.	Protocol to assess the impact of tobacco-induced volatile organic compounds on cardiovascular risk in a cross-sectional cohort: Cardiovascular Injury due to Tobacco Use study	BMJ Open	2018	
Mallock, N.,Böss, L.,Burk, R.,Danziger, M.,Welsch, T.,Hahn, H.,Trieu, H. L.,Hahn, J.,Pieper, E.,Henkler-Stephani, F.,Hutzler, C.,Luch, A.	Levels of selected carcinogens in the emissions of "Heat not Burn" tobacco products	Naunyn-Schmiedeberg's Archives of Pharmacology	2018	
Hirata, S.,Suzuki, H.,Onami, S.,Sekine, T.	Characterization of a novel tobacco vapor device using an in vivo inhalation exposure system	International Journal of Toxicology	2018	
Riggs, D. W.,Xie, Z.,Lorkiewicz, P.,Zafar, N.,Krishnasamy, S. S.,Yeager, R.,Conklin, D. J.,DeFilippis, A.,Bhatnagar, A.,Srivastava, S.	Volatile organic compounds in tobacco smoke are associated with cardiovascular disease risk	Circulation	2017	

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Ginglinger, C. G.,Mitova, M.,Maeder, S.,Smith, M.	Air quality assessment during indoor use of the tobacco heating system THS2.2	Toxicology Letters	2017	
Liu, J.,Liang, Q.,Oldham, M. J.,Rostami, A. A.,Wagner, K. A.,Gillman, I. G.,Patel, P.,Savioz, R.,Sarkar, M.	Determination of selected chemical levels in room air and on surfaces after the use of cartridge-and tank-based e-vapor products or conventional cigarettes	International Journal of Environmental Research and Public Health	2017	
Boldry, E. J.,Patel, Y. M.,Kotapati, S.,Esades, A.,Park, S. L.,Tiirikainen, M.,Stram, D. O.,Le Marchand, L.,Tretyakova, N.	Genetic determinants of 1,3-butadiene metabolism and detoxification in three populations of smokers with different risks of lung cancer	Cancer Epidemiology Biomarkers and Prevention	2017	
Peterson, L. A.,Hecht, S. S.	Tobacco, e-cigarettes, and child health	Current Opinion in Pediatrics	2017	
Shahab, L.,Goniewicz, M. L.,Blount, B. C.,Brown, J.,McNeill, A.,Udeni Alwis, K.,Feng, J.,Wang, L.,West, R.	Nicotine, carcinogen, and toxin exposure in long-Term e-cigarette and nicotine replacement therapy users	Annals of Internal Medicine	2017	
Hecht, S.,Park, S. L.,Carmella, S.,Stram, D.,Haiman, C.,Le Marchand, L.,Murphy, S.,Yuan, J. M.	Tobacco carcinogens and lung cancer susceptibility	Journal of Thoracic Oncology	2017	
Shahab, L.,Goniewicz, M. L.,Blount, B. C.,Brown, J.,McNeill, A.,Alwis, K. U.,Feng, J.,Wang, L.,West, R.	Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: A cross-sectional study	Annals of Internal Medicine	2017	
Lüdicke, F.,Baker, G.,Magnette, J.,Picavet, P.,Weitkunat, R.	Reduced exposure to harmful and potentially harmful smoke constituents with the Tobacco Heating System 2.1	Nicotine and Tobacco Research	2017	
Kim, K. H.,Szulejko, J. E.,Kwon, E.,Deep, A.	A critical review on the diverse preconcentration procedures on bag samples in the quantitation of volatile organic compounds from cigarette smoke and other combustion samples	TrAC - Trends in Analytical Chemistry	2016	
Haziza, C.,de La Bourdonnaye, G.,Merlet, S.,Benzimra, M.,Ancerewicz, J.,Donelli, A.,Baker, G.,Picavet, P.,Lüdicke, F.	Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement	Regulatory Toxicology and Pharmacology	2016	
Pazo, D. Y.,Moliere, F.,Sampson, M. M.,Reese, C. M.,Agnew-Heard, K. A.,Walters, M. J.,Holman, M. R.,Blount, B. C.,Watson, C. H.,Chambers, D. M.	Mainstream smoke levels of volatile organic compounds in 50 U.S. domestic cigarette brands smoked with the ISO and Canadian intense protocols	Nicotine and Tobacco Research	2016	
Matsumoto, T.,Katai, S.,Namiki, T.	Safety of smoke generated by Japanese moxa upon combustion	European Journal of Integrative Medicine	2016	
Bahl, V.,Weng, N. J. H.,Schick, S. F.,Sleiman, M.,Whitehead, J.,Ibarra, A.,Talbot, P.	Cytotoxicity of Thirdhand Smoke and Identification of Acrolein as a Volatile Thirdhand Smoke Chemical That Inhibits Cell Proliferation	Toxicological Sciences	2016	
Uchiyama, S.,Hayashida, H.,Izu, R.,Inaba, Y.,Nakagome, H.,Kunugita, N.	Determination of nicotine, tar, volatile organic compounds and carbonyls in mainstream cigarette smoke using a glass filter and a sorbent cartridge followed by the two-phase/one-pot elution method with carbon disulfide and methanol	Journal of Chromatography A	2015	

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Belushkin, M.,Jaccard, G.,Kondylis, A.	Considerations for comparative tobacco product assessments based on smoke constituent yields	Regulatory Toxicology and Pharmacology	2015	
Miura, N.,Yuki, D.,Minami, N.,Kakehi, A.,Futamura, Y.	A study to investigate changes in the levels of biomarkers of exposure to selected cigarette smoke constituents in Japanese adult male smokers who switched to a non-combustion inhaler type of tobacco product	Regulatory Toxicology and Pharmacology	2015	
Campbell, L. R.,Brown, B. G.,Jones, B. A.,Marano, K. M.,Borgerding, M. F.	Study of cardiovascular disease biomarkers among tobacco consumers, part 1: Biomarkers of exposure	Inhalation Toxicology	2015	
Ogden, M. W.,Marano, K. M.,Jones, B. A.,Morgan, W. T.,Stiles, M. F.	Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 2. Biomarkers of exposure	Biomarkers	2015	
Roemer, E.,Dempsey, R.,Lawless-Pyne, J.,Lukman, S.,Evans, A. D.,Trelles-Sticken, E.,Wittke, S.,Schorp, M. K.	Toxicological assessment of kretek cigarettes part 4: Mechanistic investigations, smoke chemistry and in vitro toxicity	Regulatory Toxicology and Pharmacology	2014	
Yadav, D. S.,Chattopadhyay, I.,Verma, A.,Devi, T. R.,Singh, L. C.,Sharma, J. D.,Kataki, A. C.,Saxena, S.,Kapur, S.	A pilot study evaluating genetic alterations that drive tobacco- and betel quid-associated oral cancer in Northeast India	Tumor Biology	2014	
Yuan, J. M.,Butler, L. M.,Stepanov, I.,Hecht, S. S.	Urinary tobacco smoke-constituent biomarkers for assessing risk of lung cancer	Cancer Research	2014	
Oganesyan, G.,Eimpunth, S.,Kim, S. S.,Jiang, S. I. B.	Surgical smoke in dermatologic surgery	Dermatologic Surgery	2014	Surgical smoke
Park, S. L.,Kotapati, S.,Wilkens, L. R.,Tiirikainen, M.,Murphy, S. E.,Tretyakova, N.,Le Marchand, L.	1,3-Butadiene exposure and metabolism among Japanese American, Native Hawaiian, and white smokers	Cancer Epidemiology Biomarkers and Prevention	2014	
Dolka, C.,Piadé, J. J.,Belushkin, M.,Jaccard, G.	Menthol addition to cigarettes using breakable capsules in the filter. Impact on the mainstream smoke yields of the health Canada list constituents	Chemical Research in Toxicology	2013	
Uchiyama, S.,Tomizawa, T.,Inaba, Y.,Kunugita, N.	Simultaneous determination of volatile organic compounds and carbonyls in mainstream cigarette smoke using a sorbent cartridge followed by two-step elution	Journal of Chromatography A	2013	
Maciej, G. L.	Carcinogens and toxicants in e-cigarettes	Cancer Prevention Research	2013	
Dewangan, S.,Chakrabarty, R.,Zielinska, B.,Pervez, S.	Emission of volatile organic compounds from religious and ritual activities in India	Environmental Monitoring and Assessment	2013	incense burning
Kleinstreuer, C.,Feng, Y.	Lung deposition analyses of inhaled toxic aerosols in conventional and less harmful cigarette smoke: A review	International Journal of Environmental Research and Public Health	2013	
Zhao, C.,Kim, M. K.,Kim, H. J.,Lee, S. K.,Chung, Y. J.,Park, J. K.	Comparative safety analysis of surgical smoke from transurethral resection of the bladder tumors and transurethral resection of the prostate	Urology	2013	Surgical smoke
Sarkar, M.,Muhammad-Kah, R.,Liang, Q.,Kapur, S.,Feng, S.,Roethig, H.	Evaluation of spot urine as an alternative to 24h urine collection for determination of biomarkers of exposure to cigarette smoke in adult smokers	Environmental Toxicology and Pharmacology	2013	

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Jacob, Iii P.,Raddaha, A. H. A.,Dempsey, D.,Havel, C.,Peng, M.,Yu, L.,Benowitz, N. L.	Comparison of nicotine and carcinogen exposure with water pipe and cigarette smoking	Cancer Epidemiology Biomarkers and Prevention	2013	
Mowbray, N.,Ansell, J.,Warren, N.,Wall, P.,Torkington, J.	Is surgical smoke harmful to theatre staff? A systematic review	Surgical Endoscopy and Other Interventional Techniques	2013	Surgical smoke
Park, J. P.,Zhao, C.,Shin, Y. S.,Kim, M. K.,Kim, H. J.	Is transurethral surgery for bladder tumor or BPH safe to operator?	European Urology, Supplements	2013	surgical smoke
Urban, H. J.,Tricker, A. R.,Leyden, D. E.,Forte, N.,Zenzen, V.,Feuersenger, A.,Assink, M.,Kallischnigg, G.,Schorp, M. K.	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 8: Nicotine bridging - Estimating smoke constituent exposure by their relationships to both nicotine levels in mainstream cigarette smoke and in smokers	Regulatory Toxicology and Pharmacology	2012	
Tricker, A. R.,Kanada, S.,Takada, K.,Leroy, C. M.,Lindner, D.,Schorp, M. K.,Dempsey, R.	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 5: 8-Day randomized clinical trial in Japan	Regulatory Toxicology and Pharmacology	2012	
Tricker, A. R.,Kanada, S.,Takada, K.,Martin Leroy, C.,Lindner, D.,Schorp, M. K.,Dempsey, R.	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-day randomized clinical trial of a menthol cigarette in Japan	Regulatory Toxicology and Pharmacology	2012	
Schorp, M. K.,Tricker, A. R.,Dempsey, R.	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 1: Non-clinical and clinical insights	Regulatory Toxicology and Pharmacology	2012	
Tricker, A. R.,Jang, I. J.,Martin Leroy, C.,Lindner, D.,Dempsey, R.	Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: Eight-day randomized clinical trial in Korea	Regulatory Toxicology and Pharmacology	2012	
Bodnar, J. A.,Morgan, W. T.,Murphy, P. A.,Ogden, M. W.	Mainstream smoke chemistry analysis of samples from the 2009 US cigarette market	Regulatory Toxicology and Pharmacology	2012	
Metayer, C. S.,Zhang, L.,Wiemels, J. L.,Bartley, K.,Schiffman, J.,Ma, X.,Aldrich, M.,Selvin, S.,Smith, M.,Buffler, P. A.	Effect of tobacco smoking on the risks of childhood acute lymphocytic and myeloid leukemias, by phenotypic and cytogenetic subtype	Cancer Research	2012	
Kotapati, S.,Sangaraju, D.,Walker, V. E.,Swenberg, J. A.,Tretyakova, N. Y.	Urinary biomarkers of exposure to 1,3-Butadiene and its bioactivation to DNA-reactive metabolites	Cancer Research	2012	
Park, S. C.,Ko, O. S.,Lee, S. K.,Park, J. K.	Comparison of gases produced during greenlight hps laser prostatectomy and transurethral resection and vaporization of the prostate	Journal of Urology	2012	Surgical smoke
Xie, J.,Marano, K. M.,Wilson, C. L.,Liu, H.,Gan, H.,Xie, F.,Naufal, Z. S.	A probabilistic risk assessment approach used to prioritize chemical constituents in mainstream smoke of cigarettes sold in China	Regulatory Toxicology and Pharmacology	2012	
Hertz, R.,Streibel, T.,Liu, C.,McAdam, K.,Zimmermann, R.	Microprobe sampling-Photo ionization-time-of-flight mass spectrometry for in situ chemical analysis of pyrolysis and combustion gases: Examination of the thermo-chemical processes within a burning cigarette	Analytica Chimica Acta	2012	
Zhang, Z.,Kleinstreuer, C.,Feng, Y.	Vapor deposition during cigarette smoke inhalation in a subject-specific human airway model	Journal of Aerosol Science	2012	
Hecht, S. S.	Tobacco smoke carcinogens and lung cancer		2011	
Lewin, J. M.,Brauer, J. A.,Ostad, A.	Surgical smoke and the dermatologist	Journal of the American Academy of Dermatology	2011	Surgical smoke

Studies with smoking or smoke				
Author	**Title**	**Journal**	**Year**	**Notes/ Comments:**
Gaworski, C. L.,Oldham, M. J.,Wagner, K. A.,Coggins, C. R. E.,Patskan, G. J.	An evaluation of the toxicity of 95 ingredients added individually to experimental cigarettes: Approach and methods	Inhalation Toxicology	2011	
Wang, J.,Liang, Q.,Mendes, P.,Sarkar, M.	Is 24h nicotine equivalents a surrogate for smoke exposure based on its relationship with other biomarkers of exposure?	Biomarkers	2011	

Supplemental Literature Search Results Conducted in August, 2023

Updated BD Literature Search Results (published between 1/1/2020 - 8/1/2023)

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SciPinion

SURVEY RESULTS

Science Advisory Panel for Human Health Risk Assessment

Panelist will be providing guidance to conducting a quantitative human health risk assessment for a chemical under U.S. Toxic Substances Control Act (TSCA). This will include exposure assessment (e.g., occupational, general public) and toxicity assessment (toxicity values, margin of exposure). Experience in using biomarker data (hemoglobin adducts) to support dosimetry decisions and/or Cox proportional hazards modeling is also useful.

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Appendix B: Expert Panel Engagement

SciPinion engaged an independent panel of experts to serve on a science advisory panel (SAP) using methods described in Kirman et al. (2019). The process was designed with the goal of maximizing the pool of ideal panelists, defined as the intersection of four populations, people who have expertise in the subject matter, are objective, are available to participate, and are willing to participate. Seven experts in human health exposure, toxicity, and risk assessment were identified to participate in this panel. The process for recruiting, selecting, and engaging the expert panel is described below.

Panel Recruitment

Potential candidates were identified as having relevant experience in occupational exposure assessment (and exposure limit calculation), reproductive and developmental toxicity assessment, and risk assessment using a variety of sources, including: (1) SciPinion's internal database; (2) searches for authors of recent publications on the topic of interest in online databases (e.g., Pubmed, Google Scholar); (3) searches of profiles on social media databases (e.g., LinkedIn); (4) general internet searches; and (5) referrals. Email addresses were obtained for as many potential candidates as possible. An email invitation was sent to all potential candidates, requesting interested candidates to volunteer on https://app.scipinion.com, upload a copy of their CV, and provide a brief application statement (*i.e.*, *what makes you qualified for this panel?*). SciPinion received CVs from a total of 502 applicants, 31 of which were excluded for failing to upload their CV, leaving 471 candidates to go through the next step of the process.

Panel Selection

A triple blinded process was used: (1) candidates were blinded to the review sponsor; (2) the review sponsor was blinded to the candidates and played no role in selelction; and (3) those selected for the panel were blinded to one another. Expertise data provided by the applicants and extracted from their CVs were used to rank the candidates with respect to general expertise metrics (e.g., academic degree, number of years of experience, number of publications) and topic-specific expertise metrics (e.g., CV key word counts).

Seven panel members were selected by SciPinion from the available candidates based upon the expertise metrics described above. Additional candidates were identified as potential alternates, in case a panelist is unable to complete the participation. The demographics and expertise metrics for the 7 panelists in Panel 2 are as follows:

- Country of residence: United States (7)
- Current sector of employment: Academia (2), Consulting or Retired/Past Government (4), Consulting or Retired/Past Industry (1)
- Advanced degrees: PhD (6); MS (1)

- Mean years of experience: 37±12 years
- Mean publications: 103±60

Panel Engagement

The 7 panel members were placed under contract. Email addresses corresponding to their SciPinion user accounts were verified as belonging to the experts (i.e., associated with their publication record, with their place of employment, or verified by personal communication). Charge questions were developed by SciPinion.

During the application process and throughout the peer review, panel members were blinded to the identities of their fellow panel members (identified online only by their display names of "Expert 1", "Expert 2"...). Individual responses to the charge questions are linked to the experts anonymized display names, and not to their identities, an effort intended to provide psychological safety.

The primary review material consisted of the following summary document (see Appendix A), select references from the published literature, and pdf reports that summarized the input from previous rounds. Panel members were also permitted to request additional publications and reports as needed to support their participation. The expert panel engagement was structured to have 5 rounds using a modified Delphi format (start in April of 2024, completion in June of 2024):

- *Round 1* – Panel members worked independently to read the review material (Appendix A, Section 1; select publications and reports) and answer Round 1 charge questions. 6/7 panel members completed their assignment as scheduled. One panel member was unable to continue due to other obligations (no responses submitted). An alternate was identified with similar expertise to continue in their place, and was able to complete Round 1 with a 1-week extension.
- *Round 2* – Panel members worked deliberatively to review and comment on each other's responses to Round 1 questions. All participation was conducted online (app.scipinion.com) in an anonymous manner (i.e., experts were randomly assigned display names "Expert 1", "Expert 2"...). A total of 157 comments were received during the comment rounds (Rounds 2 and 4), with all panel members participating.
- *Round 3* – Panel members worked independently to review additional material (Appendix A, Section 2; select publications and reports) and additional charge questions. All panel members completed this round as scheduled.
- *Round 4* – Like Round 2, panel members worked deliberatively to review and comment on each other's responses to Round 3 questions.
- *Round 5* – Panel members worked independently to review additional material (Appendix A, Section 3; select publications and reports) and additional charge questions. Panel members were also tasked with revisiting all previously

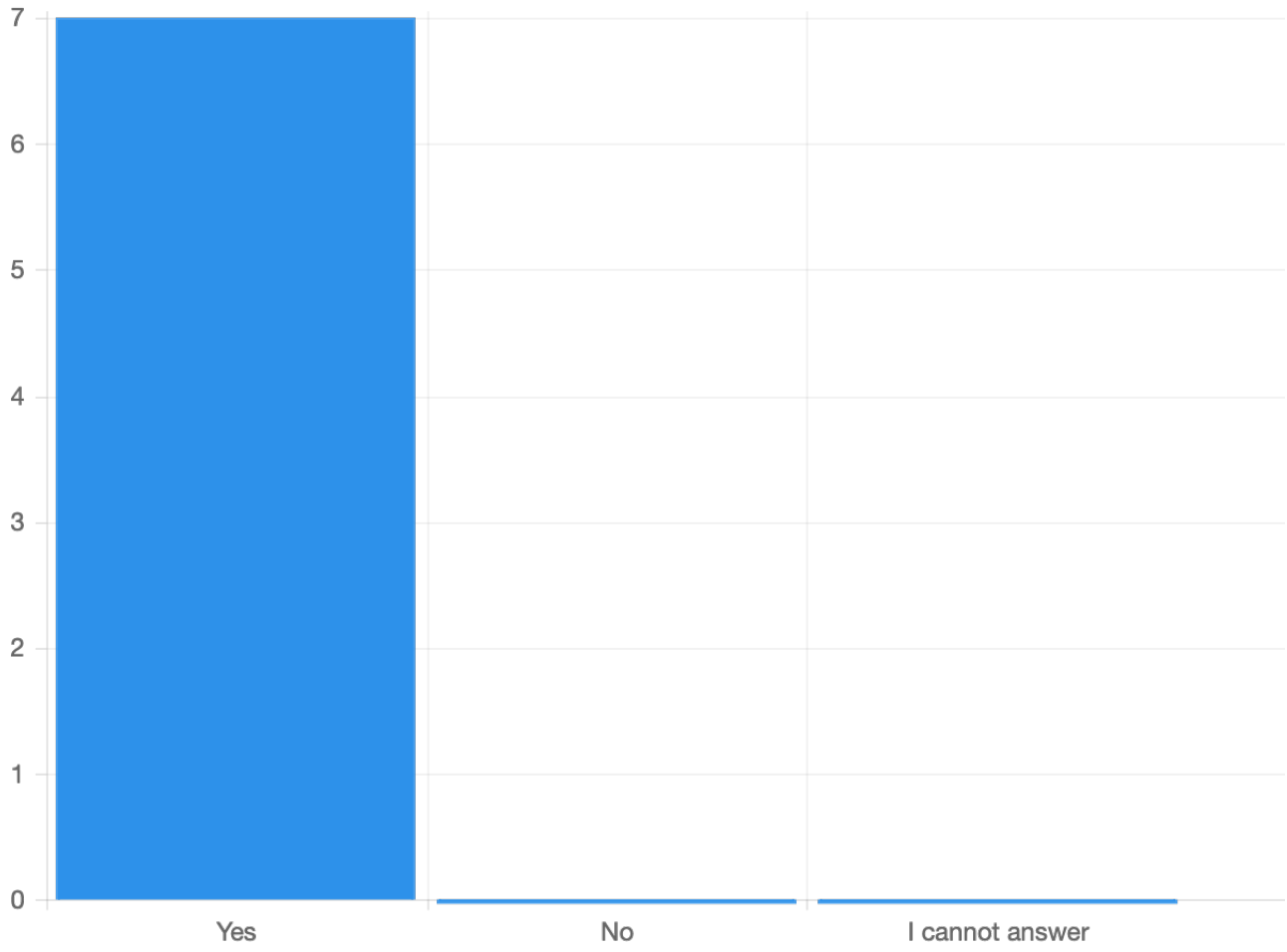
submitted responses to ensure they reflect their final answers, in case participation in Rounds 2 and 4 resulted in a change in their position. All panel members completed this round as scheduled.

All charge questions and panel member responses from this engagement are provided below.

ROUND 1 CHARGE QUESTIONS ON EXPOSURE ASSESSMENT

Result 1.1 *(ID: 6290)*
Question 1.1 *(ID: 5681)*

As summarized review material, based on a consideration of BD's emissions (>99% to air), physical chemical properties (e.g., boiling point of -4.5 degrees C), and toxicity database (almost exclusively via the inhalation pathway), a decision was made to focus efforts for the quantitative risk assessment on the inhalation pathway. Do you agree with this decision? Please explain your answer



Legend

answers: 7
skips: 0

Answer Explanations

Expert 7 Explanation
Selected Answer(s): Yes

I AGREE that the most appropriate route of (focus of) exposure for a human health risk assessment (HRA) of 1,3-BD is via the inhalation route. My opinion is based on the physical/chemical and other data and information

contained in the following documents reviewed: Summary Document (including some from the references there within); EPA 2020; EPA 2019 (Proposed Designation of 1,3-Butadiene (CASRN 106-99-0) as a High-Priority Substance for Risk Evaluation); as well as the ECHA dossier for 1,3-BD.

In addition, I would also recommend that the other, in my opinion, "less significant" (for human health risk) routes of exposure to 1,3-BD be also [quantitatively, if possible] assessed, if feasible. I say this because the U.S. EPA has mentioned these other routes (dermal, oral, via ingestion of food, etc.) in their recent documents (EPA 202 and 2019) and would, I am sure, look for these to be assessed, if they were to ever use/reference the proposed human health risk assessment for 1,3-BD.

Expert 5 Explanation
Selected Answer(s): Yes

It is clear from the review material summary that the inhalation pathway is of greatest concern. This is because inhalation exposures are the focus of the toxicology and epidemiology studies, the physical chemical properties reduce concerns for the dermal and oral routes of exposure, and the main sources of emissions show that releases into the air are the most common (i.e., combustion emissions from fires and vehicles, industrial processes and disposal).

Expert 2 Explanation
Selected Answer(s): Yes

I agree with the decision that inhalation is a primary route of exposure for 1,3- Butadiene, however data are presented as totals to various environmental media and did not discuss the methodology or how the data could.be used in BD exposure assessment. Production volume does not correspond to occupational /environmental exposure to general including.to susceptible /vulnerable population. The primary exposure sources for BD are ambient and indoor air under different settings (e.g., occupational, residential, outdoor, automobile exhaust, smoking, etc.) needs to be carefully considered based on measured monitoring data and /or validated exposure modelling approaches in any new quantitative risk assessment. Other routes of exposure such as water, soil, dermal contact and /or consumer products is of minor nature and have a very limited published information to perform scientifically justifiable quantitative health risk evaluations.

Expert 4 Explanation
Selected Answer(s): Yes

The information and citations presented in the Summary provide convincing arguments that inhalation is the dominant exposure pathway for BD in all populations that must be considered under TSCA (as outlined in US EPA 2020). Any risk assessment that hopes to be useful in supporting actions under TSCA will need to present decisions as described in Summary Table 8. Furthermore, this exposure rationale should be explicitly congruent with the conceptual model presented in US EPA (2020). Rationale for excluding specific exposure pathways must be explicit. Table 8 is a good start.

Note that mouthing behaviors in children is a clear focus of US EPA (2020), and the Summary document adresses this in a convincing manner with an appropriate citation. The MFED (2019) document is a good source.

Expert 1 Explanation
Selected Answer(s): Yes

The stated arguments appear to be sound, with the chemistry of BD dictating the most plausible route of exposure. There seems to be no evidence of important dermal in occupational settings update based on my brief independent review of the literature.

Expert 3 Explanation
Selected Answer(s): Yes

There is almost no likelihood of significant lifetime exposure through any route other than inhalation. Any additional exposure would be in the third or lower significant figure, theoretically below dependable measurement in the overall exposure assessment.

Comments (10)

SCORE 2 **Expert 1** *04/27/2024 08:12*

There seems to be little to debate here.

Some extent commented on the extent to which the decision to focus on inhalation route should be defended within EPA framework. I have not special knowledge of this specific matter, but it does appear that a sound argument (for the current audience) has already been made.

However, for my views to be even stronger, I would need to review all primary sources, which seems to be beyond the charge of this project.

SCORE 2 **Expert 2** *04/27/2024 18:47*

I agree with the decision to focus on inhalation route of exposure to humans for quantitative risk asessment. **The primary exposure sources for BD are ambient and indoor air under occupational, residential, outdoor, vehcle exhaust, smoking, etc.) that needs to be carefully considered based on measured monitoring data and /or validated exposure modelling approaches in any new quantitative risk assessment. Other routes of exposure such as water, soil, dermal contact and /or consumer products are minor and have a very limited published information to perform scientifically justifiable quantitative health risk evaluations.**

SCORE 2 **Expert 5** *04/30/2024 08:21*

I agree with Reviewer #7 that the exposure routes other than inhalation should be discussed in the final TSCA risk assessment results. In particular, the dermal route seems to be of importance to occupational workers; in EPA (2020), it is stated that "workers may be exposed via dermal routes during waste handling, treatment, and disposal". Also, oral exposures from the mouthing of toys containing BD should be discussed, as the document from the Denmark EPA (2019) presents a solid analysis of this exposure route, including laboratory testing of the migration of BD from plastic materials into saliva and sweat; they limit the amount of BD found in plastic material to 1 mg/kg plastic

(1 ppm).

SCORE 1 **Expert 1** *04/30/2024 10:31*

while I agree that it is important to discuss all routes of exposure, I struggle to see any papers on dermal exposure to BD. One article that aimed to assess BD only reports levels in the air: Airborne and Dermal Exposure to Polycyclic Aromatic Hydrocarbons, Volatile Organic Compounds, and Particles among Firefighters and Police Investigators | Annals of Work Exposures and Health | Oxford Academic (oup.com). BD was clearly on the mind of the investigators but they either did not find any on skin or, more likely based on the methods described, did not bother looking in skin. In the case of BD, it may well be that the considerations of chemistry and physics preclude consideration of dermal exposure and may be the only way that this can be "discussed". This team measured BD in dermal wipes and reported (in the abstract) that the found none... Obviously deserves a closed look but again, note that there seems to be little to nothing there: Residential environmental measurements in the National Human Exposure Assessment Survey (NHEXAS) pilot study in Arizona: preliminary results for pesticides and VOCs | Journal of Exposure Science & Environmental Epidemiology (nature.com).

SCORE 1 **Expert 3** *04/30/2024 14:12*

I concur that there is no debate here. The nature of this type of risk assessment needs to be focused on the primary route of exposure. Often, there is a single route that completely dominates the calculations, as is the case of BD. Little chance of disagreement among experts.

SCORE 2 **Expert 7** *05/01/2024 09:42*

I agree 100% that the primary route of exposure to BD that needs to be covered in the human health risk assessment (HRA) is inhalation. I am still of the opinion that the exposure routes other than inhalation should be discussed in the final TSCA risk assessment results.

SCORE 1 **Expert 4** *05/03/2024 14:33*

I'm just reiterating my comment that other routes of exposure need to be discussed in order to comport with US EPA 2020. This seems to be an opinion shared by other reviewers.

SCORE 0 **Expert 2** *05/04/2024 08:19*

SURVEY RESULTS

SCORE
1

Expert 2

05/04/2024 08:30

I recommend based on the review of summary documentation that the primary focus of shoud be on inhalation exposure patway for the future quatitative human health risk assessment. I don't see any disagreements among experts.

SCORE
0

Expert 6

05/06/2024 09:09

There seemed to be agreement that inhalation exposure will drive the risk assessment and should be the focus for the quantitative risk assessment. However, other routes of exposure should be qualitatively noted to show that they were considered. The BD concentrations in vehicles are of concern, especially on a hot summer day - everybody knows the “new car smell”. These exposures may contribute significantly to the exposure of non-occupational subjects with long commutes, and especially for infants who are most vulnerable and inherently are the first in the car before the air conditioning is on.

Result 1.2 *(ID: 6291)*
Question 1.2 *(ID: 5682)*

For assessing inhalation exposures to BD, please provide your recommendation for including the following points of exposure in the quantitative risk assessment:

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)	Total
Workplace Air	**100.00%** 7	**0.00%** 0	**0.00%** 0	**0.00%** 0	7
Ambient Air	**100.00%** 7	**0.00%** 0	**0.00%** 0	**0.00%** 0	7
Indoor Air (e.g., residence, office)	**85.71%** 6	**0.00%** 0	**0.00%** 0	**14.29%** 1	7
In-vehicle air	**71.43%** 5	**0.00%** 0	**14.29%** 1	**14.29%** 1	7
Other (please explain)	**0.00%** 0	**0.00%** 0	**50.00%** 2	**50.00%** 2	4

Answer Explanations

Expert 7 Explanation
Selected Answer(s):

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Workplace Air	1	0	0	0
Ambient Air	1	0	0	0
Indoor Air (e.g., residence, office)	1	0	0	0
In-vehicle air	1	0	0	0
Other (please explain)	0	0	0	1

My opinion is that the proposed HRA should definitely assess both the known/potential workplace and ambient air exposures to 1,3-BD.

As far as my opinion to at least consider to include both indoor air and in-vehicle air in the HRA: While is seems that existing air concentration data for both scenarios existed, they seem to be limited. However, the Summary Document (section 2.4) and the EU Risk Assessment Report (RAR) for 1,3-BD (EU 2002) present data (although, in my opinion, at very, very low concentrations) for 1,3-BD and if quantitative "toxicity" factors (e.g. inhalation unit

risk [IUR], RfD, ADI, OEL, etc.) are derived as part of the HRA, one could, I believe, fairly easily use those 1,3-BD exposure concentrations with one or more of those toxicity values to show [probably] insignificant health risk in those exposure scenarios.

Expert 5 Explanation

Selected Answer(s):

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Workplace Air	1	0	0	0
Ambient Air	1	0	0	0
Indoor Air (e.g., residence, office)	1	0	0	0
In-vehicle air	1	0	0	0
Other (please explain)				

For workplace air, consider including direct and indirect exposures and protective gear. One issue to consider in regulation is how the EPA interfaces with the standards set by the Occupational Safety and Health Administration (OSHA)? OSHA currently has standards in place for BD as follows:
Time-weighted average (TWA) limit. The employer shall ensure that no employee is exposed to an airborne concentration of BD in excess of one (1) part BD per million parts of air (ppm) measured as an eight (8)-hour time-weighted average.
Short-term exposure limit (STEL). The employer shall ensure that no employee is exposed to an airborne concentration of BD in excess of five parts of BD per million parts of air (5 ppm) as determined over a sampling period of fifteen (15) minutes. Source: https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1051

For ambient air, include exposure models that take into account the communities near point sources, such as homes located near industrial facilities or highways. Because of climate change, the area burned by wildfires has increased, so these exposures should also be considered in the exposure modeling. “The extent of area burned by wildfires each year appears to have increased since the 1980s. According to National Interagency Fire Center data, of the 10 years with the largest acreage burned, all have occurred since 2004, including the peak year in 2015” Source: https://www.epa.gov/climate-indicators/climate-change-indicators-wildfires

Expert 2 Explanation

Selected Answer(s):

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Workplace Air	1	0	0	0
Ambient Air	1	0	0	0
Indoor Air (e.g., residence, office)	1	0	0	0
In-vehicle air	0	0	1	0
Other (please				

explain)				

It is clear based on the US NHANES BD urinary biomarkers measurements data reflecting total recent exposures across all pathways is ubiquitous, and smoking remains the single largest non-occupational source (Nieto et al. 2021) and decreased by 50%, in US population over a period of 20 years (1975-2015). According to the US EPA National Emissions inventory database (EPA, NEI,2020), BD direct release in ambient air is primarily via fires (73%) and mobile sources (15%) indicating inhalation exposure as a major pathway to the general population. The major point sources of BD release and air exposures include site- specific industrial processes (EPA TRI, 2021). BD released to media other than air (e.g., water, soil) are expected to be very low since it rapidly volatilizes in the air. The occupational BD exposures for a wide variety of job categories as well as ambient air release and concentrations of BD in the US have been substantially decreasing and comparatively low (EPA AMA, 2020). Studies that measured BD concentrations in air for a variety of microenvironments in the U.S. indicate that indoor concentrations higher than outdoor. In vehicle concentrations of BD data are very limited (see review by Huy et al, 2018) to justify quantitative or semiquantitative exposure -response risk evaluations. Since exposures (and any subsequent potential risk) vary due to differences among individuals, populations, spatial and temporal scales and other factors (socio-economic) and strives to present both a central tendency and a high-end estimate, therefore, these differences need to be addressed in estimating exposure risks.

It is important to note that in general, industrial production and use of BD are relatively minor contributions to total air emissions and the emissions from production have declined steadily. Manufacturing processes as they relate to potential exposure, with
most expected to workers at the beginning of the manufacturing process and this exposure is reduced by the use of personal protective equipment.

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Expert 4 Explanation

Selected Answer(s):

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Workplace Air	1	0	0	0
Ambient Air	1	0	0	0
Indoor Air (e.g., residence, office)	1	0	0	0
In-vehicle air	1	0	0	0
Other (please explain)				

Identification of other relevant exposure pathways is outside my expertise. However, any assessment of BD with implications for TSCA will need to consider the pathways presented in US EPA (2020).

Expert 6 Explanation

Selected Answer(s):

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please

				explain)
Workplace Air	1	0	0	0
Ambient Air	1	0	0	0
Indoor Air (e.g., residence, office)	1	0	0	0
In-vehicle air	1	0	0	0
Other (please explain)	0	0	0	1

Expert 1 Explanation

Selected Answer(s):

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Workplace Air	1	0	0	0
Ambient Air	1	0	0	0
Indoor Air (e.g., residence, office)	0	0	0	1
In-vehicle air	0	0	0	1
Other (please explain)	0	0	1	0

I am not a believer in the value of semi-quantitative estimates (these are usually poorly defined) in risk assessment. Thus, if included, the focus should be on quantitative assessment only. It is clear to me that the best data will come from workplace air.

The contribution of ambient air pollution in general is hard for me to judge because ambient air measurements are typically not of personal exposure but some ecological measure that may not be strongly related to personal exposure (and hence risk). Agreement of ambient and personal exposure would need to be established to proceed.

Indoor and in-vehicle are conceptually related, are components of ambient air levels. It is not clear to me that these should be considered separately, as these situations do not seem to be create exposures that are particularly concerning, certainly not on the order of smoking or occupational exposures. Is this to focus on sources in buildings and vehicles that may not be affected by emissions in the general environment (from industrial sources, fires, vehicle, etc.)?

Hope this gives context to my responses. Happy to clarify and revise, if needed, in the following rounds of discussion.

Expert 3 Explanation

Selected Answer(s):

Inhalation exposure	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please

				explain)
Workplace Air	1	0	0	0
Ambient Air	1	0	0	0
Indoor Air (e.g., residence, office)	1	0	0	0
In-vehicle air	1	0	0	0
Other (please explain)	0	0	1	0

These are the most likely sources of chronic exposure to BD over a lifetime. Subsets within these categories (e.g., workers in restaurants (cooking air) or clubs where smoking is permitted) could be teased out as they are likely higher than others ambient or indoor air situations.

Comments (9)

SCORE **Expert 1** *04/27/2024 08:20*

1

I see agreement on lack of utility of semi-quantitative risk assessment. Summary document did lead us to believe that some sources should be excluded, but in practice it is easier to include a source and show that it may (as expected) to have negligible importance, than to argue a priori that some is not important. Maybe this is just semantics and showing that data is either very limited or exposure levels negligible is all part of quantitative risk assessment. I do not see much divergence on this question among us, just some useful suggestions for consideration during actual risk assessment.

SCORE **Expert 2** *04/28/2024 08:47*

1

I don't know what semi-quantitative risk assessment means? The coventional practice of regulatory agencies is to perform either qualitative (hazard identification), if data on exposure - response (dose-reponse) is inadequate / lacking or to conduct quantitative risk aseessment. It seems there is no debate on this issue.

SCORE **Expert 1** *04/29/2024 13:36*

2

Semi-quantitative, I understand it, is ranking of risk, like low, medium, high. This can be useful for decisions when boundaries of ranks are quantitatively defined. Otherwise, too much is left to the imagination, like the IARC monograph program's groups of carcinogenicity.

SCORE **Expert 5** *04/30/2024 09:21*

1

The purpose of TSCA is to protect the public from unreasonable risk of injury to health or the environment by regulating the manufacture, processing, distribution, use, sale, and disposal of chemicals. This act does not address pollution, which is regulated by other parts of the EPA under the Clean Air Act, Clean Water Act and the Resource Conservation and Recovery Act. Thus, a sound

argument can be made that exposures to tobacco smoke and to chemicals associated with wildfires or mobile sources are outside of TSCA's purview. On the other hand, according to EPA (2020), "TSCA§ 6(b)(4) requires EPA to determine whether a chemical substance presents an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation." The question is whether the additional exposures to BD from smoking behaviors (in vehicles or homes), wildfire activity (germane to certain geographical areas), or mobile sources (homes located near high traffic areas) exacerbate the health impacts of commercial exposures to BD. TSCA defines 'potentially exposed or susceptible subpopulation' as a group of individuals within the general population with greater susceptibility or greater exposure than the general population (paraphrased from EPA (2020)). It seems that exposures to BD resulting from smoking behaviors, mobile sources and/or wildfires concurrent with ambient air releases of BD from commercial processes would qualify as "greater exposure than the general population". Smoking behavior should be considered in the exposure modeling for occupational workers and as an additional source of BD in homes and vehicles. In the exposure modeling, BD exposures from mobile sources and wildfire activity should be evaluated, as appropriate, especially for homes located near industrial facilities.

SCORE 1 **Expert 3** *04/30/2024 14:22*

Aside from workers in BD or SBR plants (OSHA regulated), or those living in proximity to such plants, there is little to suggest that a risk assessment based on measured indoor and outdoor air levels would not be adequate for EPA's regulatory needs. The public is unaware of the presence of BD in the air and in all likelihood couldn't do anything about it if it was aware. The niche cases should be considered, but not in the context of a risk assessment for the general population.

It is rare that different sources of a contaminant result in exposures that are truly additive (one source much higher than another and thus any "arithmetic" involving these exposures is dominated in the first significant figure by the largest source.) EPA needs to take into consideration what level of effort results in an analysis that is suitable for purpose. Chasing down every minute source would be waste of EPA time and resources.

SCORE 3 **Expert 7** *05/01/2024 10:07*

My understanding (and previous use of...) semi-quantitative human health risk assessment (HRA) is categorization of health risk using a combination of exposure and toxicity (using both quantitative and qualitative data), to "rank" an estimate of human health risk as low, medium, high, etc. However, in this case, it is my opinion, that if there are reliable exposure data for (one or both) indoor air and in-vehicle, they can easily be "assessed" quantitatively using those exposure data and any available/derived "toxicity factor(s) for BD. I believe that if this done/attempted in the HRA, it will pre-

empt any questions as to why there were not assessed in the HRA.

SCORE
1

Expert 2

05/02/2024 09:51

Thank you for the clarification and expanding the discussion on the value of semi-quantitative risk assessment in exposure ranking and categorization of health risks and I aggree with it. However, it's value in and significance for regulatory policy-making in quantitive human health risk assessment is questionable. Although. the discussion of semi- quatitative risk asessment based on solid expsure -response data is desirable but it becomes cotroversial and debateable, if used alone in regulatory context.

SCORE
1

Expert 2

05/04/2024 08:52

I am restating my opinion that the semi-quantitative human health risk assessment 1, 3-BD would be of little value in regulatory context except for categorization of health risks. I think all of us agree that qualitative discussion of all other sources of exposure may be appropriate but if acutal measuremts and biomonitoring data are insufficient or lacking, it will be negligible importance. I recommend that the semi- quantitative human health risk assesment should not be encouraged. Overall, it seems all of the experts agree on this issue.

SCORE
0

Expert 6

05/06/2024 09:22

I do agree that one should consider quantitative risk assessment for all exposure types where sufficient data are available and state that accurate exposures data are missing for xyz exposures situations.

Result 1.3 *(ID: 6292)*
Question 1.3 *(ID: 5683)*

As summarized in review material, a number of other exposure pathways are considered to be either negligible (relative to inhalation) or incomplete. Please provide your recommendation for considering additional exposure pathways in the risk assessment.

Other Pathways	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)	Total
Dermal contact with liquid BD solutions (workers)	**0.00%** 0	**0.00%** 0	**100.00%** 7	**0.00%** 0	7
Ingestion of groundwater	**0.00%** 0	**14.29%** 1	**71.43%** 5	**14.29%** 1	7
Ingestion in the diet from food contact materials	**0.00%** 0	**0.00%** 0	**85.71%** 6	**14.29%** 1	7
Ingestion from consumer products (e.g., gum, mouthing of toys)	**0.00%** 0	**0.00%** 0	**85.71%** 6	**14.29%** 1	7
Other (please explain)	**0.00%** 0	**0.00%** 0	**100.00%** 3	**0.00%** 0	3

Answer Explanations

Expert 7 Explanation
Selected Answer(s):

Other Pathways	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Dermal contact with liquid BD solutions (workers)	0	0	1	0
Ingestion of groundwater	0	0	0	1
Ingestion in the diet from food contact materials	0	0	0	1
Ingestion from consumer products (e.g., gum, mouthing of toys)	0	0	0	1
Other (please explain)	0	0	1	0

For dermal contact with liquid 1,3-BD, it's my opinion that because liquid 1,3-BD evaporates (volatilizes) so rapidly because of its Vp, it could cause "frostbite" (as stated in the Summary Document and other references I

consulted). This [potentially painful] health hazard may not be known to users (persons exposed) to the liquid and, based on my past industrial experience with other chemicals for which this is a known/potential health hazard, I recommend that users (people potentially contacting liquid 1,3-BD) be at least warned of this health hazard.

Regarding my selection as "other" for the ingestion of groundwater; ingestion in the diet; and ingestion from consumer products: While I AGREE that these routes of exposure would more than highly likely to be negligible in the context of human health risk, some quantitative exposure data seem to be available based on my review of the Summary Document and EPA 2020. Therefore, if reliable, quantitative exposure data for 1,3-BD are able to be found, one could, I believe, fairly easily use those 1,3-BD exposure concentrations with one or more of those toxicity values to show [probably] insignificant health risk in those exposure scenarios.

Expert 5 Explanation

Selected Answer(s):

Other Pathways	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Dermal contact with liquid BD solutions (workers)	0	0	1	0
Ingestion of groundwater	0	0	1	0
Ingestion in the diet from food contact materials	0	0	1	0
Ingestion from consumer products (e.g., gum, mouthing of toys)	0	0	1	0
Other (please explain)				

As discussed in the review materials, oral and dermal exposures are unlikely to occur, so quantitative risk estimates are not necessary for these exposure pathways. They should, however, be discussed qualitatively. In particular, health risks from mouthing of toys is usually an alarming issue and should be fully discussed, with the reasons behind not doing a quantitative assessment explained.

Expert 2 Explanation

Selected Answer(s):

Other Pathways	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Dermal contact with liquid BD solutions (workers)	0	0	1	0
Ingestion of groundwater	0	0	1	0
Ingestion in the diet from food contact materials	0	0	1	0
Ingestion from consumer products (e.g., gum, mouthing of toys)	0	0	1	0
Other (please explain)	0	0	1	0

Due to the chemical/ physical properties of 1,3-butadiene, inhalation is the most likely route of exposure, and a dermal exposure pathway for workers during unloading and sampling is likely to be negligible. Therefore, it is

recommended that the dermal route should not be included for quantitative/semiquantitative risk assessment; and furthermore, the evaluation of dermal exposure through contact with the material in liquid form may not be necessary for the commercial stage of commercial products that use synthetic rubber as a raw material in their manufacturing process.1,3-butadiene has been measured at very low levels in rubber or plastic of food packaging and has been found only occasionally in food samples. Overall, exposure to 1,3-butadiene through consumption of food, drinking water and/ or consumer products is expected to be very low in comparison to exposure through. inhalation of contaminated air (ATSDR, 2012), therefore, they should not be considered as major pathways of exposure in health risk evaluation of BD.

Expert 4 Explanation
Selected Answer(s):

Other Pathways	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Dermal contact with liquid BD solutions (workers)	0	0	1	0
Ingestion of groundwater	0	0	1	0
Ingestion in the diet from food contact materials	0	0	1	0
Ingestion from consumer products (e.g., gum, mouthing of toys)	0	0	1	0
Other (please explain)				

Dermal contact with BD contained in liquids has been described in both the Summary and in US EPA (2020). That contact with such liquids would result in frostbite is a convincing argument that exposure in any population would be unlikely.

Any BD in groundwater is likely to be volatilized rapidly and is unlikely to be available for skin contact or present in sufficient concentration to present a hazard from ingestion. The current hazard assessments are derived from inhalation exposure. I would assume from US EPA (2020) that an attempt will be made to derive dermal and oral dose response assessments through existing dose conversion methodologies. Thus, there may be a need to consider oral and dermal exposure in a semi-quantitative manner (using a dose conversion methodology) to apply inhalation risk estimates to these pathways.

Arguments for excluding oral exposure from food and mouthing behaviors are similar to those for groundwater. From US EPA (2020) I would expect that some scoping assessment of these pathways will be done, and compared with an oral dose response assessment.

I did not review the ECHA documents, but I suggest that as recent evaluations they may be particularly germane.

Expert 1 Explanation
Selected Answer(s):

Other Pathways	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Dermal contact with liquid BD	0	0	1	0

solutions (workers)				
Ingestion of groundwater	0	0	1	0
Ingestion in the diet from food contact materials	0	0	1	0
Ingestion from consumer products (e.g., gum, mouthing of toys)	0	0	1	0
Other (please explain)				

I was not presented with evidence that other sources listed here make material contribution to personal exposure. It is impossible to not discuss them, of course, but this may well be best handled qualitatively, in a sense that potential exposure is compared to major sources quantitatively and on these grounds ruled to be only useful to consider qualitatively in risk assessment, for the sake of completeness only.

Expert 3 Explanation

Selected Answer(s):

Other Pathways	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Dermal contact with liquid BD solutions (workers)	0	0	1	0
Ingestion of groundwater	0	1	0	0
Ingestion in the diet from food contact materials	0	0	1	0
Ingestion from consumer products (e.g., gum, mouthing of toys)	0	0	1	0
Other (please explain)	0	0	1	0

Groundwater is likely to contribute a very small amount of BD, so it should not be excluded completely. The other unlikely sources have been adequately addressed and may be excluded without issue.

Comments (6)

SCORE 3 **Expert 1** *04/27/2024 08:31*

Ingestion, consumer products (esp. toys), and groundwater sources must obviously be mentioned even if a priori they expect to contribute little more other than to focus attention on situations where there may actually be a tangible risk, i.e. inhalation in workplaces. Otherwise, some (me) would argue that general air pollution is a non-issue unless one showed that levels of exposure are comparable to those considered unacceptable in workplace atmosphere.

SCORE 2 **Expert 2** *04/27/2024 19:17*

Overall, exposure to 1,3-butadiene through consumption of food, drinking water and/ or consumer products is expected to be very low in comparison to exposure through. inhalation pathway, therefore, they should not be considered as major pathways of exposure in human health

risk evaluation of 1,3- BD. Furthermore, limited published exposure information on these pathways may not meet rigorous scrutiny of existing exposure information for considering it in quantitative risk evaluation.

SCORE
0

Expert 3

04/30/2024 14:24

I concur with experts one and two and have considered this issue in my comment to point 1.2

SCORE
3

Expert 7

05/01/2024 10:08

I agree that these routes of exposure (groundwater, diet/food and consumer products) to BD would probably be very minor, especially in comparison to inhalation exposure, BUT they should at least be addressed in the human health risk assessment of BD. I am still of the opinion that dermal contact with the liquid BD should have a qualitative discussion of the health hazard of frostbite - especially for workers.

SCORE
2

Expert 2

05/04/2024 09:01

I recommend that other routes exposure than inhalation are of minor nature , uneless and otherwise thoroughly documented based on peer-reviewed published information and publically available data.All other exoposure pathways of 1, 3-BD than inhaltion, may deserve qualitative assessment only.

SCORE
0

Expert 6

05/06/2024 09:28

I agree that these types of exposures are neglectable and can bee excluded from the quantitative risk assessments.

Result 1.4 *(ID: 6293)*
Question 1.4 *(ID: 5684)*

Please provide your recommendation for considering human health receptors in the risk assessment for BD.

Receptors	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)	Total
BD manufacture workers (adult)	**100.00%** 7	**0.00%** 0	**0.00%** 0	**0.00%** 0	7
Downstream workers; e.g., SBR workers (adult)	**100.00%** 7	**0.00%** 0	**0.00%** 0	**0.00%** 0	7
General public (consider of all relevant age stages)	**71.43%** 5	**14.29%** 1	**14.29%** 1	**0.00%** 0	7
Other (please explain)	**50.00%** 1	**0.00%** 0	**50.00%** 1	**0.00%** 0	2

Answer Explanations

Expert 7 Explanation
Selected Answer(s):

Receptors	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
BD manufacture workers (adult)	1	0	0	0
Downstream workers; e.g., SBR workers (adult)	1	0	0	0
General public (consider of all relevant age stages)	1	0	0	0
Other (please explain)				

Based on my review of the supplied documents, including the Summary Document, EPA 2020, EPA 2019; the EU RAR (2002), I AGREE with what is stated in section 2.7 of the Summary Document, as well as what is presented in Table 8 of the Summary Document. In my opinion, considering all three categories of these human health receptors is strongly supported in the text of the Summary Document.

Expert 5 Explanation
Selected Answer(s):

Receptors	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please

				explain)
BD manufacture workers (adult)	1	0	0	0
Downstream workers; e.g., SBR workers (adult)	1	0	0	0
General public (consider of all relevant age stages)	1	0	0	0
Other (please explain)	1	0	0	0

For the general public, special consideration should be given to residents of the homes of smokers, including second-hand smoke exposures.

Another set of human health receptors who should be evaluated is people who drive cars or trucks for a living, e.g., taxi drivers, delivery men/women, semi-truck drivers. Since in-vehicle air is of concern, this is a group who may be differentially exposed. Further, the smoking behavior of these divers should be included in the evaluation.

Expert 2 Explanation

Selected Answer(s):

Receptors	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
BD manufacture workers (adult)	1	0	0	0
Downstream workers; e.g., SBR workers (adult)	1	0	0	0
General public (consider of all relevant age stages)	1	0	0	0
Other (please explain)				

Given the major BD inhiation exposure pathways under site-specific conditions (manufacturing/operations, handling and transporting) and potential downstream exposure to occupational workers including to other users in a wide variety of job categories, the focus on quantitative health risk assessment is warranted but it should be based on critical review and reanalysis of both, human and experimental animal published studies/ data. Ambient air exposure to BD monitoring data (EPA AMA, 2020) and air modeling data near industrial facilities could be useful and justify its use in quantitative exposure- potential adverse health effects risk evaluation for general population. Exposure data for all relevant life- stages such as pregnant women, infants and children and/or disproportionately highly exposed subpopulation are very limited and needs to be carefully considered and it may deserve only qualitative discussion unless justified otherwise with discussion of uncertainties, strengths and weaknesses of the supporting data.

Expert 4 Explanation

Selected Answer(s):

Receptors	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
BD manufacture workers (adult)	1	0	0	0
Downstream workers; e.g.,	1	0	0	0

SBR workers (adult)				
General public (consider of all relevant age stages)	1	0	0	0
Other (please explain)				

Note that the US EPA TSCA risk assessors will be obliged to consider all the pathways and receptors that they describe in the conceptual model (US EPA, 2020). Consideration does not necessarily result in inclusion of a receptor or a pathway in the quantitative risk assessment. The same may be said of any assessment that would be useful for actions under TSCA.

Arguments for focus on more relevant receptors and exposure pathways are supported by the Summary document; for example, there are useful discussion and figures on BD biomarkers in smokers vs. nonsmokers, as well as on the decreasing trend for smoking in the US population. The decreasing exposure to workers (e.g. Figure 4) is also a useful point. The Summary makes useful points on the decreasing exposure to BD in the US generally given controls in BD manufacturing and use, as well as public health measures to decrease exposure to cigarette smoke. (BTW, I found the inclusion of Figure 5 to be distracting rather than illuminating).

The Summary discussions of decreasing BD emissions in the US are cogent. Note that given the increasing incidence of wildfires in the US and Canada, I would expect reviewers of any BD risk assessment to express concern about this source of release. Obviously TSCA has no risk management authority for smoke exposure, but I can see it as an increasing source of BD in ambient air.

Expert 1 Explanation
Selected Answer(s):

Receptors	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
BD manufacture workers (adult)	1	0	0	0
Downstream workers; e.g., SBR workers (adult)	1	0	0	0
General public (consider of all relevant age stages)	0	0	1	0
Other (please explain)				

I believe that all risk assessments must be quantitative at their core. Only once the calculations were carried out and the uncertainty appraised, can we judge whether a particular group has negligible risk. There seems to be as good of data as we can have for quantitative risk assessment that is informative for occupational settings.

It is less clear to me that exposure assessment is adequate for risk assessment of general population, but it is likely that an inference of plausible risk can be made from occupational settings to the worst-case exposure assumption in general population: after all a worker is just a person from general population who happens to be near the sources and more highly exposed. At this stage, one can perhaps argue whether a more refined assessment of general population is warranted or whether evidence indicates that that any plausible risks, even if precisely quantified, would be below threshold of concern. Given what I was asked to read to date, it seems that there will be no need to do quantitative risk assessment for general population due to low exposures, but it is important to

verify once risk assessment for occupational settings is complete.

If there is evidence of excess risk to general population of adults, I would then see it essential to consider risk to children. One can start with risk to children under the assumption that they are more vulnerable, but I need to better understand whether BD has ever been implicated in childhood leukemias (or any other outcomes).

Expert 3 Explanation
Selected Answer(s):

Receptors	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
BD manufacture workers (adult)	1	0	0	0
Downstream workers; e.g., SBR workers (adult)	1	0	0	0
General public (consider of all relevant age stages)	0	1	0	0
Other (please explain)	0	0	1	0

Based on the information contained in the summary, there may be significant BD exposure contributors in cities and other areas away from manufacturing centers. Therefore, I conclude that they should be explicitly included in the assessment.

Comments (7)

SCORE **Expert 1**
1

04/27/2024 12:25

The only issue that seems worth debating regarding this question is how smoking and second-hand smoke are treated. These entail BD exposure but are in no way equivalent to BD exposure in pure form. A useful analogy of the complexities (based on my experience) is PAHs: they seem to have different effects when present on their own than when considered as part of complex mixture in tobacco smoke. Thus, I would not favor any risk assessment of BD based on smokers and second-hand smoke exposure, because subtracting the effect of everything else in tobacco smoke to isolate the effect of BD seems both impossible and unnecessary (if occupational data is of high quality). Smoking is a potential confounder here; secondhand smoke less likely so given that it is an order of magnitude less toxic than smoking.

The idea of conducting an evaluation of BD risk among professional drivers is interesting, but I am not certain how it would be separate from any evaluation of occupational risks. Any OEL would apply to any workplace, not just those where most of BD evidence comes from. In any case, it may be useful what assessment of exposure to BD among professional divers reveals, but I struggle to see how this can be essential to assessment of risk due to BD per se,

SCORE **Expert 2**

4

The major BD inhiation exposure pathways for site-specific conditions such asmanufacturing/operations, handling and transporting and potential downstream exposure to occupational workers including to other users in a wide variety of job categories should be the focus on quantitative health risk assessment. Ambient air exposure to BD monitoring data and air modeling data near industrial facilities could be useful and justify its use in quantitative exposure-potential adverse health effects risk evaluation for occupational workers and general population. Exposure data for all relevant life- stages such as pregnant women, infants and children and/or disproportionately highly exposed subpopulation are very limited and needs to be carefully considered and it may deserve only qualitative discussion unless justified otherwise with discussion of uncertainties, strengths and weaknesses of the supporting data.

04/29/2024 08:35

SCORE

Expert 3

0

As I have mentioned in comments to previous sections, smokers and workers need to be considered as sub-groups and separated from the risk assessment for the general population.

04/30/2024 14:27

SCORE

Expert 7

0

I agree in that it is very much worth exploring the relationship between BD exposure concurrent exposure to smoking and second-hand smoke are treated with regards to impact on the heath hazard(s), and ultimate human health risk of exposure to BD in these sub-populations. My one caveat to this is if such "specific" data (for smokers/second-hand smoke exposure populations) can be found and found to be reliable

05/01/2024 10:09

SCORE

Expert 4

2

The TSCA risk assessors will be obliged to consider the "general population" in their assessment. This will include consideration of life stage susceptibility.

05/03/2024 14:53

SCORE

Expert 2

2

I am reietrating my recommendation and agree with other experts that major human health receptors for 1, 3- BD exposures are occupational workers (under different operating condtions) , ambient air exposure to general population including to sensitive sub-population (if only reliable quality data available) should be the focus of quantitative human health risk asessment of BD. All the confounding risk factors, identified - smoking / other chemical's exposure)and unidentified needs to be accounted for/ controlled in perfoming 1, 3- BD huan health risk assessment.

05/04/2024 09:18

SCORE

Expert 6

05/06/2024 09:40

0 I agree with most of the above. BD exposure of major concern are for occupational workers, ambient air exposure to general population (id quality data are available).

Result 2.1 *(ID: 6294)*
Question 2.1 *(ID: 5685)*

Noncancer: Based upon Table 9 in the review material, two noncancer endpoints have been considered by nearly all regulators and risk assessors for the human health risk assessment of BD over the past several decades. A review of the recent literature published for this chemical has not resulted in the identification of any additional health endpoints. Please provide your recommendation for including the following noncancer endpoints in the quantitative risk assessment.

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)	Total
Fetal body weight changes in rodents	**83.33%** 5	**0.00%** 0	**16.67%** 1	**0.00%** 0	6
Ovarian atrophy in rodents	**71.43%** 5	**14.29%** 1	**14.29%** 1	**0.00%** 0	7
Other (please explain)	**0.00%** 0	**25.00%** 1	**25.00%** 1	**50.00%** 2	4

Answer Explanations

Expert 7 Explanation
Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Fetal body weight changes in rodents	1	0	0	0
Ovarian atrophy in rodents	1	0	0	0
Other (please explain)				

I agree with what is presented in Table 9 of the Summary Document, as well as the summary presented charge question 2.1 (as seen above) regarding these two (2) non-cancer endpoints to be the main focal points for non-cancer endpoints associated with exposure to 1,3-BD for assessment in the proposed 1,3-BD HRA.

One point the SciPinion Panel may want to discuss is regarding the endpoint of ovarian atrophy as noted in female mice (NTP, 1993). I agree that it was noted at all exposure doses from the lowest exposure dose (6.25 ppm) onwards ovarian atrophy was increased [from TCEQ 2015: "Statistically significant increases in the incidence of

ovarian atrophy were observed in all exposure groups following lifetime exposures. The LOAEL for ovarian atrophy was observed at the lowest exposure level (6.25 ppm, 6 h/day, 5 days/week, for 2 years"]. However, the EU RAR (2002) states the following states the following with regards to that study (as it pertains to determining a study NOAEL for ovarian atrophy): "Ovarian atrophy was seen in a 2-year study in the mouse, at the lowest exposure concentration tested, 6.25 ppm, and uterine atrophy developed after 9 months exposure to 200 ppm and above. The effects on the ovary at 6.25 ppm were seen only towards the end of the 2-year exposure period, when there would be general senescence of the reproductive system." I only bring this up for possible discussion because I don't know enough about mouse reproductions, etc. to verify the possibility of reproductive senescence as is stated in the EU RAR and how it may/may not apply to the use of these data (i.e. the 6.25 ppm) for the [eventual] derivation of the non-cancer toxicity factor (i.e. choosing to start with a NOAEL or LOAEL, for example) developed for the ovarian atrophy endpoint in the HRA (or maybe use BMD modeling).

Expert 5 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Fetal body weight changes in rodents	1	0	0	0
Ovarian atrophy in rodents	1	0	0	0
Other (please explain)				

Fetal body weight changes in rodents was not the most sensitive effect found in the EPA's IRIS assessment of 2002, however, new approaches to BMDS modeling and UF application are reasons for revisiting this endpoint. Ovarian atrophy in rodents appears to be the most sensitive effect in mice.

The fundamental question is whether sufficient evidence exists to support that BD is a chemical that is likely to cause some form of noncancer toxicity in humans and requires regulation. The toxicity literature presented in the background materials suggests that this is the case. Further, because reproductive and developmental effects are seen in mice and rats, it is possible that they may also occur in humans. Although no human toxicity data are available for these effects, BD biomarkers show evidence of BD exposures in both smokers and nonsmokers in the U.S. Therefore, an updated RfCc for BD should be calculated and published.

Expert 2 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Fetal body weight changes in rodents	1	0	0	0
Ovarian atrophy in rodents	1	0	0	0
Other (please explain)				

On review of the Table 9 and cited references, I agree with the statement that the two noncancer endpoints have been considered by the regulatory authorities (Health Canada & US EPA) and ATSDR/ CDC as published. However, in order to include them in the quantitative risk assessment reaffirming or rejecting their conclusions, a systematic review of all peer-reviewed published literature and publicly available information for noncancer adverse effects needs to be considered in any revaluation efforts in revision risk assessment of 1, 3 - Butadiene (BD). Any new health risk assessment of 1, 3 - Butadiene environmental/occupational exposure need to meet the criteria or stand the scrutiny of an independent expert peer -review panel (e.g.; SAB and/or NAS) and serious consideration of public comments. Reevaluation of health risk assessment should be based on the recently published SOPs of the EPA IRIS Program recommendations (U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (2022). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-22/268, 2022). The TSCA section 26(h) text to assert that "when making a decision based on science, [EPA is required to] use information, procedures, methodologies, and protocols consistent with the best available science." and to consider "the degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented.

Expert 4 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Fetal body weight changes in rodents	1	0	0	0
Ovarian atrophy in rodents	1	0	0	0
Other (please explain)	0	0	0	1

Generally I found the Summary discussion of hazard assessment to be inadequate and unconvincing. The statement that the US EPA's assessment is more than 20 years old is not useful. The point is that US EPA itself, as well as other authoritative bodies, have made substantial changes in using improved methodologies for all phases of risk assessment. The hazard identification, that is attributing likely health endpoints to BD exposure will have to be redone by US EPA and any other risk assessors who wish to contribute to TSCA considerations of BD.

It is important that the discussion of hazard characterization (particularly choice of studies and endpoints for quantitative risk assessment) be completely transparent. I found the statements in the Summary document as written to be unconvincing; for example, "no new studies that would support departing from the historically used human and animal endpoints" is not supported by any demonstration, citations, or discussion. The following quote does not provide sufficient support for the "no new studies" conclusion: "A literature search was conducted to identify additional endpoints/studies that could serve as the bases for the noncancer and cancer risk assessment for BD (Appendix A)." Appendix A does not give the beginning and end dates of the search (although presumably 08/23). I did not see in Appendix A a method or set of criteria to determine how citations were sorted and excluded. I did not see any discussion of how the decision was made that "For the noncancer assessment, no additional studies or endpoints were identified to supercede the selection of fetal body weight changes and ovarian atrophy as the bases for risk assessment". From what is written in the Summary document there is no way to tell what other studies or endpoints may have been evaluated and excluded. Transparency is needed in the

selection of critical endpoints and studies.

The US EPA (2002) document was written before release of the US EPA final Cancer Guidelines in 2005; any revised hazard identification and dose response assessment will be obliged to follow those Guidelines. The Guidelines have implications for assessment of effects other than cancer. For example, evaluation of non cancer effects attributed to BD should involve consideration of mode of action (MOA) for those endpoints and if those MOA are relevant to human health hazard.

Points in the Summary on low dose extrapolation are generally well taken, but are insufficiently described. There are now several guidance documents both for determining the point of departure and for extrapolating below that point. US EPA will be obliged to follow at least their own benchmark dose guidance as well as the 2014 Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation (EPA/100/R-14/002F). Application of this guidance will involve consideration of points raised in the Summary on species difference in metabolism and activation of BD. Application of this and other US EPA Reference Dose, Reference Concentration guidance will make clear that uncertainty factors used in US EPA (2002) are outdated.

Motwani and Tornqvist (2014) describes a reasonable approach to interspecies extrapolation for BD data.

BTW please note that statements such as this in the Summary "This research is not controversial." immediately arouses my suspicions.

Expert 6 Explanation
Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Fetal body weight changes in rodents				
Ovarian atrophy in rodents	0	1	0	0
Other (please explain)	0	1	0	0

What about acute exposures induced neurological effects?

Expert 1 Explanation
Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Fetal body weight changes in rodents	0	0	1	0
Ovarian atrophy in rodents	0	0	1	0
Other (please explain)	0	0	1	0

I am unsure of the relevance of these outcomes in humans, esp. ovarian atrophy. Fetal growth restriction is related to smoking of mothers during pregnancy and this correlated with BD exposure (since it is in tobacco smoke). However, I am not aware of any results on fetal growth restriction in humans due to BD per se. Admittedly, I am not a toxicologists, so my view of these matters is to be downplayed.

Expert 3 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Fetal body weight changes in rodents	1	0	0	0
Ovarian atrophy in rodents	1	0	0	0
Other (please explain)	0	0	0	1

There are no new studies in rodents available.

Comments (9)

SCORE 1 **Expert 1** *04/27/2024 12:38*

I did a very cursory search on perinatal exposure and birth outcomes in humans (epidemiolog) and BD. Found these two:
retinoblastoma and perinatal exposure: https://pubmed.ncbi.nlm.nih.gov/24280682/
birth weight: https://pubmed.ncbi.nlm.nih.gov/33778332/
A systematic literature search obviously is a must, not limited to studies in rodents. I am not arguing that these endpoints should be considered based on papers that I found but they sure have to be discussed in any comprehensive risk assessment.

SCORE 1 **Expert 3** *04/30/2024 15:43*

My area of expertise is exposure assessment, however, I concur that a complete review of the literature since the previous assessment must be undertaken. The relevance of the rodent data to the human assessment must also be taken into consideration as it appears that mice are much more susceptible to BD's effects than humans are. (Cancer endpoints)

SCORE 0 **Expert 5** *05/01/2024 07:46*

Thanks to Expert #4 for pointing out the EPA's 2014 Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation (EPA/100/R-14/002F). This document provides the guidance needed to address the Interspecies uncertainty factor for BD which is complicated by the difference in metabolic activation

between mice and humans. In this document, the interspecies uncertainty factor (typically a factor of 10) is divided into an interspecies extrapolation factor based on toxicokinetic information (EFAK) and an interspecies uncertainty factor for toxicodynamics (UFAD), since no data were available to develop an interspecies extrapolation factor for this. The example for vinyl chloride in Appendix A.1.2 illustrates a method that may be of use in evaluating BD, using the data from Motwani and Tornquist 2014 to inform the value of EFAK.

SCORE
1

Expert 5

05/01/2024 08:18

I agree with Expert #4 that information on the literature search results for BD toxicity studies is important to the identification of other health endpoints that may need to be considered. Based on the information given to us in the Summary document, one could surmise that fetal body weight and ovarian atrophy in rodents were indeed the only/best endpoints to evaluate for the noncancer risk assessment. However, further reading of the EPA 2020 scoping document reveals other potential noncancer endpoints, such as, genetic, irritation/corrosion, immune, neurological, cardiovascular, endocrine, gastrointestinal, hematological, hepatic, musculoskeletal, nutritional and metabolic, ocular and sensory, renal, respiratory, skin and connective tissue. In addition, Expert #1 located epidemiology studies on retinoblastoma and birth effects associated with BD exposure. To be fully transparent, a summary of studies showing these effects were observed as the result of BD exposures should be made available, and criteria for the exclusion of these endpoints should be clearly articulated.

SCORE
1

Expert 7

05/01/2024 10:21

While both fetal body weight in rodents and ovarian atrophy in rodents have been the major adverse health effect endpoints assessed in previous assessment/document, I also agree that a complete literature search be completed to make sure that there are no other potentially "critical" endpoints of BD toxicity to be assessed in the human health risk assessment of BD.

I am still in agreement with Expert # 1 regarding the known/potential relevance of ovarian atrophy as a human health endpoint for BD exposure. Expert #1 stated: "I am unsure of the relevance of these outcomes in humans, esp. ovarian atrophy." I only bring the endpoint of ovarian atrophy (only observed in mice) up for possible discussion because I don't know enough about mouse reproductions, etc. to verify the possibility of reproductive senescence in mice as a "confounding/influencing factor" for the observation of an association between BD exposure and ovarian atrophy. I would just like this enpoint's "relevance" investigated more by an expert(s) in that field.

SCORE
0

Expert 2

05/02/2024 13:09

I agree with that the two noncancer endponts of toxicity (fetal body weight and ovarian atrophy) in rodents are the major advrese effects of BD exposue. However, the large quantitative differences in the metabolism of BD and potency of critical epoxide mtatbolites must be accounted for when rodent toxicity responses are extrapolated to humans. Human relevance of the both noncancer endpoints identified in rodents is not well scientifically articulated and is inadquate in the past risk assessments. Givan inter- and intra species differences as well as human variation in reproductive biology in the general and sensitive subpopulations, a careful literature search and critical review by independent experts in reproductive biology/ toxicology is warrented. Again, smoking in women of rproductive age, pregnant women , aging individuals as well as other poential exposure confounding factors likely to impact the quaantitative human health risk evaluation of 1, 3 - BD.

SCORE
0

Expert 4

05/03/2024 15:02

I appreciated expert 5's comments on the UF.

SCORE
1

Expert 2

05/04/2024 10:43

I recommend and agree with other experts that the two noncancer endponts of toxicity (fetal body weight and ovarian atrophy) in rodents are the major advrese effects of BD exposure and are appropriate for quantitative risk assessment. However, discussion of human health relevance of these obervations in rodents supported by mod(s) of action/ mechanisms of advrese outcomes is highly warrented given species- to -species differences in metabolism and toxicokinetics of 1,3- BD..

SCORE
0

Expert 6

05/06/2024 10:03

I agree, that a comprehensive literature review is needed to judge none-cancer risk, such as preterm birth birth weight and ovarian atrophy. The studies cited for these are quiet old and it is reasonable to assume that more recent studies will be very informative.
Further, I like to reiterate considering to include assessment of neurological effects from acute/accidental exposures.

Result 2.2 *(ID: 6295)*
Question 2.2 *(ID: 5686)*

Cancer: Based on Table 9 of the review material, regulatory agencies and risk assessors have historically relied upon epidemiology mortality data and rodent cancer bioassays for estimating the cancer potency of BD. Please provide your recommendation for including the following cancer potency datasets in the quantitative risk assessment.

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)	Total
Mortality data from epidemiology studies (e.g., SBR cohort)	**100.00%** 7	**0.00%** 0	**0.00%** 0	**0.00%** 0	7
Cancer incidence data from rodent cancer bioassays	**57.14%** 4	**14.29%** 1	**14.29%** 1	**14.29%** 1	7
Other (please explain)	**50.00%** 2	**0.00%** 0	**0.00%** 0	**50.00%** 2	4

Answer Explanations

Expert 7 Explanation
Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Mortality data from epidemiology studies (e.g., SBR cohort)	1	0	0	0
Cancer incidence data from rodent cancer bioassays	0	0	0	1
Other (please explain)				

Based on my review of the relevant documents provided with the Round 1 Charge, as well as other documents I consulted for my review, I agree with the 5 main bullet points (as well as the sub-bullet points) presented in Section 3 of the Summary Document. In my opinion, the use of the updated SBR (worker) cohort epidemiological data (e.g. Valdes-Flores et al., 2022) should, as noted in Section 3, be strongly considered (speaking as a non-epidemiologist....) as the best data available (e.g. human data used for human HRA) for assessing cancer endpoints of inhalation to 1,3-BD. I believe that the use of high-quality, reliable epidemiological data are supported for assessing cancer endpoints in humans because of their use in Carcinogenic Health Hazard Classification by U.S. NTPs' 15th Annual RoC (2021): "1,3-Butadiene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies." and IARC: "There is *sufficient evidence* in humans for the carcinogenicity of 1,3-butadiene." and IARC (Vol. 97; 2008) Overall

evaluation: "1,3-Butadiene is *carcinogenic to humans (Group 1)*."

I selected "Other" for cancer incidence from rodent bioassays because I believe that the cancer studies in rodents (especially in mice; NTP 1993) should be discussed in the HRA and reasons for not using those data for the carcinogenic health risk assessment (i.e derivation of an inhalation cancer toxicity value; IUR, for example) should be outlined and discussed. Just as an example for support of this opinion is from the 2002 EU RAR, Section 4.1.2.8.3: "Summary of carcinogenicity: In relation to investigations in experimental animals, the carcinogenicity of butadiene has been studied in rats and mice. There is a marked species difference in the susceptibility of rodents to the carcinogenic properties of butadiene. In the mouse, butadiene is a potent, multi-organ carcinogen. The carcinogenic response is typified by early onset of tumours and the development of rare tumour types. Tumour development occurs at relatively low exposure concentrations and is also seen following a relatively short exposure to higher butadiene concentrations. All the evidence indicates that a genotoxic mechanism is involved. In comparison, in the rat, the one available study shows a lower tumour frequency, fewer tumour types, mainly of a benign nature, with effects seen at exposure concentrations 2-3 orders of magnitude higher than in the mouse. The tumour type in the rat suggests that hormonal influences may play a role in the carcinogenic response, and thus a non-genotoxic mechanism may underlie the tumour formation in this species."

Expert 5 Explanation
Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Mortality data from epidemiology studies (e.g., SBR cohort)	1	0	0	0
Cancer incidence data from rodent cancer bioassays	1	0	0	0
Other (please explain)				

The fundamental question is whether sufficient evidence exists to support that BD is carcinogenic in humans and requires regulation. The toxicity literature presented in the background materials suggests that this is the case, showing evidence of leukemia (and other cancers) in humans and multiple tumors in mice. Further, the Department of Health and Human Services, International Agency for Research on Cancer (IARC), and EPA have all determined that BD is a human carcinogen. BD biomarkers show evidence of BD exposures in both smokers and nonsmokers in the U.S., raising concerns about potential health impacts. BD is thought to be a non-threshold carcinogen. It metabolizes to DNA-reactive epoxide intermediates. These intermediates can cause genetic alterations in proto-oncogenes and tumor-suppressor genes. The linear model used by EPA (2002) and Health Canada (2000) aligns with this mechanism, as even minor exposure may impact gene integrity. The Cox proportional hazard model used by Valdez-Flores et al. (2022) is also a good option for dose-response modeling. Therefore, an updated cancer slope factor assessment for BD should be derived and published, using updated styrene-butadiene rubber (SBR) cohort data and adjusting for smoking behaviors.

Leukemia in humans exposed to BD has been found in the SBR workers cohort which has been studied since 1944. Two confounders that may affect dose-response modeling of the relationship between DB and leukemia are the co-exposure to styrene by SBR workers, which has been measured, and the smoking behaviors of the SBR

workers, for which data has not been collected. The EPA IRIS assessment of 2002 used a linear model by Heath Canada that adjusted for age, calendar year, years since hire, race, and exposure to styrene, but assumed no confounding by smoking. It seems illogical not to account for smoking, and it is unclear why data on smoking behavior was not collected in this cohort. The assumption being made by not adjusting for smoking is that smoking behaviors are the same for all workers in the SBR cohort. Therefore, risk estimates from the modeling would be biased high, with steeper slopes for models unadjusted for smoking.

It may be possible to adjust the results of dose-response modeling to reflect in general the smoking behaviors of the SBR workers. The summary materials present NHANES biomarker data on BD for smokers vs. nonsmokers, implying that these data can be of use in evaluating carcinogenicity and mortality resulting from BD exposures in this cohort. In addition, the CDC published a report in 2011 on cigarette smoking prevalence among working adults, stratified by socioeconomic variables and by industry and occupation group in the U.S. for the years 2004-2010 (source: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6038a2.htm#tab2). For example, for manufacturing workers, age-adjusted cigarette smoking prevalence was reported to be 23.2% (95% CI=21.9%-24.5%); for production workers, it was 26.1% (95% CI=24.6%-27.7%).

Expert 2 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Mortality data from epidemiology studies (e.g., SBR cohort)	1	0	0	0
Cancer incidence data from rodent cancer bioassays	1	0	0	0
Other (please explain)	1	0	0	0

On review of the summary of information in Table 9 and a cursory preliminary review of epidemiology studies cited as reported in results and conclusions sections of the authors, claiming a positive relationship between 1,3- Butadiene exposure and all leukemia among North American synthetic rubber polymer workers needs to be reevaluated by an independent panel of epidemiology experts. They should have access to review the original set of exposure and cancer mortality data for individual subjects' exposure history to BD and cancer mortality/incidence and other health outcomes for analysis to reconfirming or rejecting the authors conclusions. Most of the subjects in the SBR cohort were also exposed to styrene and potentially to other chemicals (e.g., benzene, diethyldithiocarbamate). Uncertainty remains about the BD exposure alone that might be responsible for the observed excesses and about the role of and systematically accounting for all confounding factors including smoking data. There is a clear need to disentangle the exposure and mortality of the 1,3- butadiene and styrene since their cancer hazard identification and cancer classification designation have been controversial over the years among regulatory authorities, international organizations and stakeholders. Furthermore, integration of human and animal evidence evaluating available mechanistic data information for biological possibility of cancer by application of key characteristics of known human carcinogens needs to be considered in revaluation of 1, 3- Butadiene risk assessment. There are species differences in metabolism and potential sources of nonlinearity for each key events (MOAs) that can affect extrapolations from high -to- low dose exposures. Therefore, MOAs for BD needs to be assessed using Hill

Criteria and human relevance framework. In order to perform new toxicological review and health risk assessment, it is important develop scientifically sound and credible transparent documentation.

Expert 4 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Mortality data from epidemiology studies (e.g., SBR cohort)	1	0	0	0
Cancer incidence data from rodent cancer bioassays	1	0	0	0
Other (please explain)	0	0	0	1

Generally I found the Summary discussion of hazard assessment to be inadequate and unconvincing. The statement that the US EPA's assessment is more than 20 years old is not useful. The point is that US EPA itself, as well as other authoritative bodies, have made substantial changes in using improved methodologies for all phases of risk assessment.

The hazard identification, that is attributing likely health endpoints to BD exposure, will have to be redone by US EPA and any other risk assessors who wish to contribute to TSCA considerations of BD. The US EPA document was written before release of the US EPA final Cancer Guidelines in 2005; any revised hazard identification and dose response assessment will be obliged to follow those Guidelines. It is unlikely that the hazard identification of "carcinogenic to humans" will change. The US EPA 2005 Guidelines (unlike IARC methods), however, do specify that the categorization can be specific to an exposure scenario or population; such as, "carcinogenic by inhalation at exposure concentrations above x mg/m3".

Other applications of US EPA (2005) for BD will include these: consideration of MOA, consideration of relevance of animal observations and MOA for potential adverse effects in humans, determination of a point of departure (POD) using recent guidance, application of low dose extrapolation based on consideration of MOA.

For BD, it will be necessary to determine if mutation is an early key event in a MOA. For some risk assessors, the fact that there are some positive data for mutagenicity in a variety of assays is sufficient to warrant a decision that there is a mutagenic MOA and that linear low dose extrapolation is the only appropriate choice (I am not one of those risk assessors). Note that determination of a mutagenic MOA generally results in the application of an age dependent adjustment factor (ADAF) for early life exposure; this would be relevant to BD exposures in consumer and general population evaluations. A thorough review and evaluation of the genotoxicity testing data should be undertaken, employing the most recent OECD guidance. I noted in US EPA (2002), that many assays relied on measurement of sister chromatid exchange (SCE). This endpoint is no longer in common use, and OECD declined to update SCE assay guidance. It also appeared that many endpoints noted in humans were cytogenetic (micronucleus and others). Most assessors schooled in genotoxicity accept that cytogenic effects and some mutations arise through a multi-step process.

The US EPA applied a so-called "effect level extrapolation factor" of two fold to the cancer unit risk, and it notes that guidance on application was in progress. However, US EPA did not pursue and publish guidance on such a

factor. I am unsure whether these factors were applied in assessments other than that for BD. As far as I could tell, this extrapolation factor was used for BD to account for the possibility of other cancers than those significantly increased in the SBR cohort. I think this was also prompted by the multi-site nature of the neoplasms observed in the animal studies and by the apparent increased susceptibility in female rodents. This may still be a consideration for the current assessment.

In the Summary there is no discussion of the critical study and endpoint for the human studies. The Summary mentions only that the SBR cohort used in US EPA (2002) has been updated. I would assume that the faults in the studies not used by US EPA remain reasons for exclusion as the critical study. Nevertheless choice of the data set for dose response assessment will need to include explicit rationales for the decisions.

Valdez-Flores et al (2022) presents results of updates of the an expanded SBR cohort, including female workers, and additional years of follow up. It applies recent models and analyses of confounders and covariates. The paper also describes cancers other than leukemia, such as bladder - urinary tract tumors. Analyses were done to investigate three potential sources of uncertainty not considered in earlier evaluations: (1) exposure lag and windows of exposure to assess whether all exposures to BD are important to the observed cancer response; (2) the shape of the exposure-response relationship to assess the presence of meaningful departures from linearity (or log-linearity); and (3) an aggregate endpoint (leukemia and/or urinary/bladder cancer) to provide an assessment of total risk. The results are well-discussed and supported.

Note that generally speaking, cancer incidence data are preferred to cancer mortality data.

Expert 6 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Mortality data from epidemiology studies (e.g., SBR cohort)	1	0	0	0
Cancer incidence data from rodent cancer bioassays	1	0	0	0
Other (please explain)	1	0	0	0

We may want to include the huge body of mode of action data.

Expert 1 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Mortality data from epidemiology studies (e.g., SBR cohort)	1	0	0	0
Cancer incidence data from rodent cancer bioassays	0	0	1	0
Other (please explain)				

I am strongly in favor of replying on human data for risk assessment in humans, esp. when it is robust as seems to be the case here. The main point is that in epi we have the correct species and realistic exposures, which cannot be assured in the lab. One has to mention lab results but they should play a secondary role, filling the gaps that human data cannot (not certain that there are such gaps in epidemiology of BD).

Expert 3 Explanation

Selected Answer(s):

Endpoint	Should be included in the quantitative risk assessment	Should be included semi-quantitatively	Can be excluded from the quantitative risk assessment (qualitative discussion only)	Other (please explain)
Mortality data from epidemiology studies (e.g., SBR cohort)	1	0	0	0
Cancer incidence data from rodent cancer bioassays	0	1	0	0
Other (please explain)	0	0	0	1

The recent reevaluations have shown large interspecies differences, therefore, the human data should be paramount in the risk assessment.

Comments (10)

SCORE 3 **Expert 1** *04/29/2024 11:00*

I do not thing that anyone will argue that all available information should NOT be used, including any in vitro results. But on balance, when there is high-quality data on humans, this should surely dominate the decision, because it is based on the correct species experiencing relevant levels of exposure for human health risk assessment.

SCORE 2 **Expert 3** *04/30/2024 15:45*

I completely agree with expert 1.

SCORE 3 **Expert 7** *05/01/2024 10:30*

From my reading of the other Expert's comments, it seems that the use of solid, reliable human data (epidemiological data) for estimating the cancer potency of BD should definitely be used. I completely AGREE. I also agree that the newer/follow-up epidemiology data need to be critically reviewed and examined by an epidemiologist(s) for reliability and use for the cancer potency of BD. Lastly, a comprehensive review of available published (and unpublished) literature should also be undertaken. I also think that any in vitro/in vivo genotoxicity assay data, as well as the limited data available from bioassay's in rodents be used in the overall assessment of cancer potency of BD in humans the the human health risk assessment.

SCORE
-1

Expert 2

05/02/2024 12:35

On review of the summary of information & Table 9 as well as a review of epidemiology studies cited , showing a positive relationship between 1,3- Butadiene exposure and all leukemia among North American synthetic rubber polymer workers are the best available studies and appropriate. However, these studies need to be reevaluated by an independent panel of epidemiology experts. They should have access to review the original set of exposure and cancer mortality data for individual subjects' exposure history to BD and cancer mortality/incidence and other health outcomes for reanalysis. Most of the subjects in the SBR cohort were also exposed to styrene and potentially to other chemicals (e.g., benzene, diethyldithiocarbamate). Uncertainty remains about the BD exposure alone that might be responsible for the observed excesses and about the role of and systematically accounting for all confounding factors including smoking data. There is a clear need to disentangle the exposure and mortality of the 1,3- butadiene and styrene since their cancer hazard identification and cancer classification designation have been controversial over the years among regulatory authorities, international organizations and stakeholders. Furthermore, integration of human and animal evidence evaluating available mechanistic data information for biological possibility of cancer by application of key characteristics of known human carcinogens needs to be considered in revaluation of 1, 3-Butadiene risk assessment. There are species differences in metabolism, mutagenic potency and potential sources of nonlinearity for each key events (MOAs) that can affect extrapolations from high - to- low dose exposures. Therefore, MOAs for BD needs to be assessed using Hill Criteria and human relevance framework. In order to perform new toxicological review and health risk assessment with scientifically sound and credible transparent documentation. **I don't see disagreement on this issue.**

SCORE
1

Expert 4

05/03/2024 15:11

I agree with Expert 7's comment that hormonal influences may contribute to the cancer MOA in the rat.

SCORE
2

Expert 4

05/03/2024 15:14

I agree with Expert 5 that it is illogical not to account for the effect of smoking on the cancer mortality.

SCORE
0

Expert 1

05/04/2024 06:40

I am unsure that the extent of re-analysis suggested by expert 2 is either needed or realistic to undertake. It seems a measure of last resort if there is strong evidence that published papers but not underlying data are fatally flawed.

I also do not agree with invocation of Professor Bradford Hill's work in a way that he never intended it. Causal reasoning moved beyond that old paper as have the courts. In a sense, they are not criteria that can be rigorously applied because they were never meant to function as such, and Hill knew it.

SCORE 1

Expert 2

05/04/2024 12:36

I agree with and recommend that solid and reliable epidemiological data and any other new epi. data/ information for estimating inhalation unit risk is appropriate and a need for carefully examine and review by experts in epidemiology..The published rodent cancer bioassy data, genotoxicity , biomarkers data including mode(s) of action/ mechanisms of carcinogenrsis information should be critically r reviewed. I also recommend that besides, linear cancer dose -response analysis which is commonly presented by EPA , non- linear dose- response analyasis should be performed and presented as per recommendations of the US EPA 2005 cancer risk assessment guidelines . In principle, I agree with the Expert 1 that re-analysis is either not needed or realistic to undertake. However, if the epidemilogial data are the driver in derivation of inhalation cancer unit risk (most likely the case) and used in regulatory policy- making, then in my opinion, scientific integrity of the underlying data is highly critical ,. I agree with the comment of Expert 1 regarding the use of Bradford Hill criteria and request to sggest what are the scientifically accepted criteria/ measures one could be use to ensure the quality of human epidemiological/ animal studies.

SCORE 0

Expert 1

05/05/2024 09:29

I cannot endorse strongly enough expert 2 on the dire need to model non-linear and threshold effects using the best available statistical tools. Some are easy to use, so please apply them and collaborate with statisticians who mastered these techniques.

SCORE 0

Expert 6

05/06/2024 10:06

Based on my understanding of the other Expert's comments, it appears crucial to utilize solid, reliable human data (epidemiological data) to estimate the cancer potency of BD. I fully concur with this standpoint. Additionally, I agree that newer/follow-up epidemiological data should undergo thorough scrutiny to ensure their reliability and suitability for assessing the cancer potency of BD. Moreover, I believe that incorporating any available in vitro/in vivo genotoxicity assay data, along with the data from bioassays in rodents, is essential for the overall risk assessment of BD's cancer potency in humans.

ROUND 3: EXPOSURE ASSESSMENT

Result 3.1 *(ID: 6351)*
Question 3.1 *(ID: 5722)*

Based on the input received in Round 1 of this review, there appears to be general agreement within the panel on the exposure pathways proposed for the risk assessment (see Table 8 of the Round 1 Review Document). Please indicate if you would like to see any changes made to this table.

Expert 1

> The table looks fine. I have no specific suggestions if its aim is to argue for quantitative assessment via inhalation only.

Expert 4

> Table 8 looks OK.

Expert 6

> I think Table 8 very nicely summarized the panels opinion that exposure via inhalation is main route of exposures. Accidental spills of liquid BD are by nature almost impossible to quantify. Residual BD in food from packaging seem neglectable assuming subsequent cooking will essentially remove BD. Although I am not aware of any study of BD requesting in fat, or fatty food, given its hight lipophilicity.

Expert 5

> I have no changes to Table 8 to suggest at this time. However, as was discussed in Round 1 of this review, exposure routes other than inhalation should be qualitatively discussed in the final TSCA risk assessment results. In particular, oral exposures from the mouthing of toys containing BD should be discussed, as the document from the Denmark EPA (2019) presents a solid analysis of this exposure route, including laboratory testing of the migration of BD from plastic materials into saliva and sweat; Denmark has set a limit for the amount of BD found in plastic material to 1 mg/kg plastic (1 ppm).

Expert 7

> I agree with both the "Yes" and "No" answers in the Table 8 column "Evaluation in Risk Assessment" . I do still think that the human health risk assessment needs to at least mention the potential for frostbite after dermal contact with the liquid BD. In my opinion, it would be very nice if everyone using a particular chemical used the appropriate PPE/exposure controls when using ANY chemical. However, that does not happen in real-life. This will be a risk assessment and people reading/using the assessment should be aware of exposure to the liquid and the potential for this adverse health hazard to be realized using a qualitative assessment (again, because not everyone will use the appropriate exposure reduction/elimination precautions).

Expert 2

> No, I don't see any reasons to change Table 8 of the Round 1 of the Review Document **except on the Page 2 of the Table 8 under column heading "Evaluation in Risk Assessment" the last entry for Smoking Inhaltion which says Yes (semi- quantitative), request to delete (" semi-quantitative"). I am not sure what semi- quatitative resk assessment means.**

Expert 3

> I do not see the need to change Table 8.

Comments (4)

SCORE **Expert 2** *05/21/2024 08:00*

3

I think that all Experts agree not to change the Table 8 of the Round 1 Review Document on the exposure pathways proposed for the risk assessment of 1, 3 BD.

SCORE **Expert 3** *05/27/2024 04:04*

0

I concur

SCORE **Expert 7** *05/29/2024 07:21*

0

I fully agree with the exposure pathways for the risk assessment in Table 8.

SCORE **Expert 6** *05/31/2024 05:02*

0

Seems all agree with Table 8 and removing the term “semi-quantitative”.

Result 3.2 *(ID: 6352)*
Question 3.2 *(ID: 5723)*

In Section 1 of the Round 3 Review Document, several equations are provided for quantifying exposure, noncancer hazard, margin of exposure, and cancer risk. Please indicate if you would like to see any changes made to any of the equations.

Expert 1

> I am not an expert on these equations (but they seem familiar) so will defer to others.

Expert 4

> No changes to equations needed.

Expert 6

> These equations look good to me.

Expert 5

> For Eq. 4, please define C, and define what (NC or C) means as a subscript for HE.
>
> In this document, BR is presented as a Breathing Ratio, a Breathing Rate and as a Breathing Rate Ratio. All 3 terms are used, and I am unclear on how these terms are defined and if they are the same or calculated differently. For any ratio, when both the numerator and the denominator are in the same units, then the ratio is unitless, but a breathing rate would have units, like m3/day (e.g., Table 2-8 of Round 3 Summary Document). When the term "ratio" is included, then the terms being compared in the numerator and denominator need to be specified.

Expert 7

> Both the equations for HQ and MOE look fine. However, I would like to see both HQ and MOE equations "extended" to show that the HQ looks to be < 1 and the MOE looks to be >/= 100 for "acceptable" excess risk due to exposure to BD. Also, how will HEC be calculated from the HE (eq.4). For the HE, why 78 years vs 70 for the cancer endpoint? For eq. 4, where is "C" defined? Units? Where will PFs be found or derived? CEFIC? Not sure about calculating acute exposures - is the way described what is generally used? Lastly, can the BR (unitless) be defined? I am not familiar with this input (I am familiar with "breathing rate" in m3/hr, for example, but not a "breathing rate ratio" that is unitless).

Expert 2

> No changes are needed to any of the equations.which are pretty standard ones used by the US EPA and other US regulatory agencies.

Expert 3

> HE is defined parenthetically in Section 1 as "(duration-specific average daily concentration or lifetime

average daily concentration, ppm continuous)". From the equations, I believe that HE is the lifetime (or daily) dose of BD (C is undefined in the equation, but I assume that it is concentration of BD in air). this could be clarified if it is meant for anyone other than this panel.

The equations are standard and acceptable.

Comments (5)

SCORE **Expert 4** *05/21/2024 13:44*

0

Re comments from Expert 7, I agree to a point. I noted later in this section that both the HQ and MOE are useful characterizations of risk and should be presented. The extent to which either of these values is acceptable is generally a matter of risk policy / risk management.

SCORE **Expert 2** *05/22/2024 08:17*

0

The equations are standard , accepted and used by the regulatory agencies . No changes are needed.

SCORE **Expert 5** *05/23/2024 05:28*

1

I agree that the equations are acceptable with the caveat that some of the terms need to be better defined, as indicated by myself and Experts #3 and #7. Regarding Expert #7's point to show the health benchmarks of the HQ < 1 and the MOE >/= 100, just a note that the MOE benchmark could be different than 100 depending on the analysis of uncertainties. See my comments in reference to question 3.3 where I quote page 7 of TSCA's 2022 Trichloroethyene document where the chronic MOE=30 and the acute MOE=10. (Source: https://www.epa.gov/system/files/documents/2023-01/TCE_Final%20Revised%20RD_12-21-22-FINAL-v2.pdf)

SCORE **Expert 3** *05/27/2024 04:06*

0

No additional comments needed.

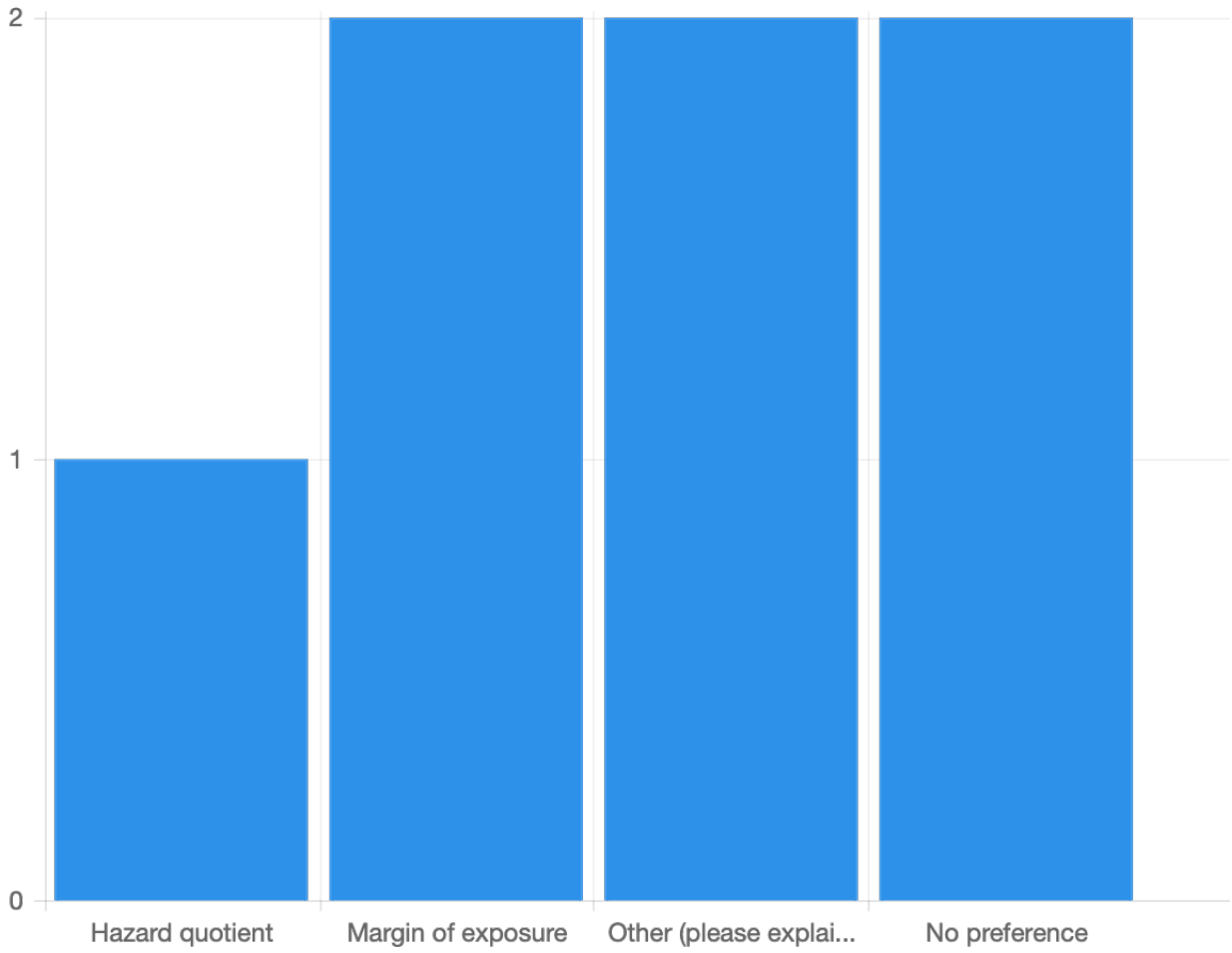
SCORE **Expert 7** *05/29/2024 07:31*

2

I agree the these equations are very much the standard for human health risk assessments. All I want to make sure of is the definition of MOE. From the referenced EPA document for TCE, it looks to me that the MOE is defined as the PoD (NOAEL, BMDL)/estimated or known human exposure for that scenario.

Result 3.3 *(ID: 6353)*
Question 3.3 *(ID: 5724)*

For the noncancer assessment, please indicate if you prefer the characterization is performed in terms of hazard quotient (Eq.1) or margin of exposure (Eq.2).



Legend

Hazard quotient: 1
Margin of exposure: 2
Other (please explain): 2
No preference: 2

answers: 7
skips: 0

Answer Explanations

Expert 1 Explanation
Selected Answer(s): No preference

not my area of expertise. for me to help, you need to develop arguments for and against these choices.

Expert 4 Explanation
Selected Answer(s): Other (please explain)

These are both easily calculated, so there is no need to choose one over the other. Both values are informative and can serve in characterizing potential risk. Risk management choices can be (and are) supported by each value under differing circumstances of problem formulation, and under differing regulatory mandates.

Expert 6 Explanation

Selected Answer(s): Other (please explain)

I think we should include both since each will be important.The margin of exposure (MOE) is more data oriented and of interest to understand other old and new studies while the hazard quotient including several uncertainty factors are the 'final' product of interest to policy makers and regulators.
Including both allows a readers to better understand our 'opinion' process.

Expert 5 Explanation

Selected Answer(s): Hazard quotient

I prefer the HQ as it compares a human exposure estimate to a human safe level, rather than the MOE which compares an animal POD to a human exposure estimate. (Note, an exception is when the POD is from human data.) The noncancer hazard quotient (HQ) is calculated by comparing a human exposure estimate to a human safe level, i.e., a Reference Value (RfV), and the HQ is intended to be health protective for sensitive humans. When the RfV is derived, it accounts for any uncertainties that exist between humans and the animal species from which the point of departure (POD) is estimated. During the development of an RfV, uncertainty factors are thoughtfully considered and based on available data whenever possible, accounting for interspecies variation, intraspecies variation, subchronic to chronic extrapolation, LOAEL to NOAEL extrapolation and database deficiencies. HQ values greater than 1 are of concern.

The margin of exposure (MOE) is calculated by comparing an animal (POD) to a human exposure estimate, not a direct comparison of like entities, unlike the HQ. An MOE greater than 100 is generally considered to be acceptable, as it covers the default uncertainty of 100 that could exist for the interspecies and intraspecies uncertainty factors, but does not account for other uncertainties, nor for the use of data derived uncertainty factors. The MOE of 100 is a default benchmark that is not based on data that is directly relevant to the chemical being evaluated and is not the product of a thoughtful review and consideration of uncertainties.

Having said all of this, I found the following text in a TSCA document on TCE that discounts my argument above about the default MOE of 100 (which I am leaving here as it is still true for some assessments). Based on the TSCA language, I see very little difference between the TSCA application of an MOE vs. a standard HQ. I still prefer the HQ over an MOE as I like the fact that it is a human to human comparison, and I believe the interpretation is more transparent and easier to present and understand. The TSCA document reads: "The MOEs are compared to a benchmark MOE. The benchmark MOE accounts for the total uncertainty in a POD, including, as appropriate: (1) the variation in sensitivity among the members of the human population (i.e., intrahuman/intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4) the uncertainty in extrapolating from a lowest observed adverse effect level (LOAEL) rather than from a NOAEL. A lower benchmark MOE (e.g., 30) indicates greater certainty in the data (because fewer of the default uncertainty factors (UFs) relevant to a given POD as described above were applied). A higher benchmark MOE (e.g., 1000) would indicate more uncertainty for specific endpoints and scenarios." (Source: https://www.epa.gov/system/files/documents/2023-01/TCE_Final%20Revised%20RD_12-21-22-FINAL-v2.pdf)

Expert 7 Explanation
Selected Answer(s): Margin of exposure

In my opinion, the most current scientific/toxicological literature generally uses the MOE (or MOS) for the characterization of noncancer risk. I would, based on my experience like to have the health risk assessment use MOE (or MOS; i.e. where the numerator has already been modified with appropriate adjustment/safety factors and the denominator is the HEC and then the MOS looks to be > 1 (vs the MOE which is > 100).

Expert 2 Explanation
Selected Answer(s): No preference

I prefer Margin of Exposure , commonly used in evaluation of noncancer heath risk assessments of chemicals to derive RfVs (RfC or RfDs by the US EPA and Hazard Quotient is used for relative risk evaluation of exposure-response to diffrent receptors.

Expert 3 Explanation
Selected Answer(s): Margin of exposure

The nature of the risk is more easily described by margin of exposure.

Comments (6)

SCORE 2 **Expert 2** *05/21/2024 08:20*

I think we have a fairly good agreement to include both the equations'(Eq.1 and Eq.2) for performing noncancer risk assessment of of 1,3- risk assessment, My preference is to use the MOE approach as it has been commonly used by the US EPA for air toxics risk evaluations.

SCORE 1 **Expert 4** *05/21/2024 13:46*

I reiterate my point that both values should be calculated and presented. The differences and applications between the HQ and MOE would form part of the risk characterization discussion of a revised butadiene document.

SCORE 1 **Expert 5** *05/23/2024 05:36*

I think it is fine to present both values. I reiterate my point that, based on the TSCA language, there is very little difference between the TSCA application of an MOE vs. a standard HQ, because uncertainties are considered for both derivations. The Trichloroethene document I have been quoting only shows the MOE and does so for acute and chronic noncancer effects. The HQ is generally calculated for chronic effects. Overall, I still prefer the HQ over an MOE as I like the fact that it is a human-to-human comparison.

SCORE
1

Expert 3

05/27/2024 04:08

Since the question asked for a preference, I chose MOE, but agree completely that both are easily calculable and understood in the regulatory community.

SCORE
1

Expert 7

05/29/2024 07:35

In my opinion, I still think that the most current scientific/toxicological literature generally uses the MOE for the characterization of noncancer risk. However, with that being said, I am fine with the presentation of both HQ and MOE in the assessment for noncancer risk.

SCORE
0

Expert 6

05/31/2024 05:08

Looks like most agree that using both would be best.

Result 3.4 *(ID: 6354)*
Question 3.4 *(ID: 5725)*

In Section 2.1, several data sources are proposed for characterizing the concentration of BD in workplace air, ambient air, indoor air, and in-vehicle air. Please indicate if you feel there are other data sources that should be considered. Also, please indicate if any of the data sets you identify should supersede those proposed, or used as supporting data.

Expert 1

> theses seem to be the right sources.
>
> have you considered OSHA IMIS data? it does not seem to have much of BD (https://academic.oup.com/annweh/article/60/4/432/2196116?login=false#95637304, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3589950/) but I am always surprised when I look at what OSHA measures.

Expert 6

> What about the BD exposure from the mono and polymer work studies in the Chez Republic Albertini et al?
> We may also consider historic trends of
> mean and max exposures.

Expert 5

> I have very limited experience with exposure modeling and related datasets, therefore, I have no data sources to propose beyond what is presented in the Round 3 Summary Report.

Expert 7

> I have reviewed the sources of, and exposure data from, Section 2.1. They seem to me to be appropriate (i.e. available from the published literature) for characterizing the concentrations of BD in the various exposure scenarios. I am not familiar with any additional, relevant exposure data for BD for those scenarios in the published/available literature - HOWEVER, that does not mean there are none available - I would turn to the other experts for their knowledge on this.

Expert 2

> I agree with the proposed data sources to characterize the concentration of 1,3 -BD in the workpllace air, ambient air, indoor air, and in-vehicle air. I didn't find any other relevant published or publically available data that could be considered.

Expert 3

> The proposed data sources are acceptable for this risk assessment.

Comments (4)

SCORE

1

Expert 1

05/22/2024 07:52

I think that we all agree that the major data sources were captured but some may emerge as the report is crafted and one always have to keep on eye o papers that are new or bring grey literature to light.

SCORE
0

Expert 2

05/22/2024 08:20

The proposed data sources appropiate and acceptable .

SCORE
1

Expert 3

05/27/2024 04:13

I concur with experts 1 and 2. Additional data sources would presumably only affect the overall exposure assessment if they were significantly different, suggesting local or point sources that may not be appropriate for a population based risk assessment.

SCORE
2

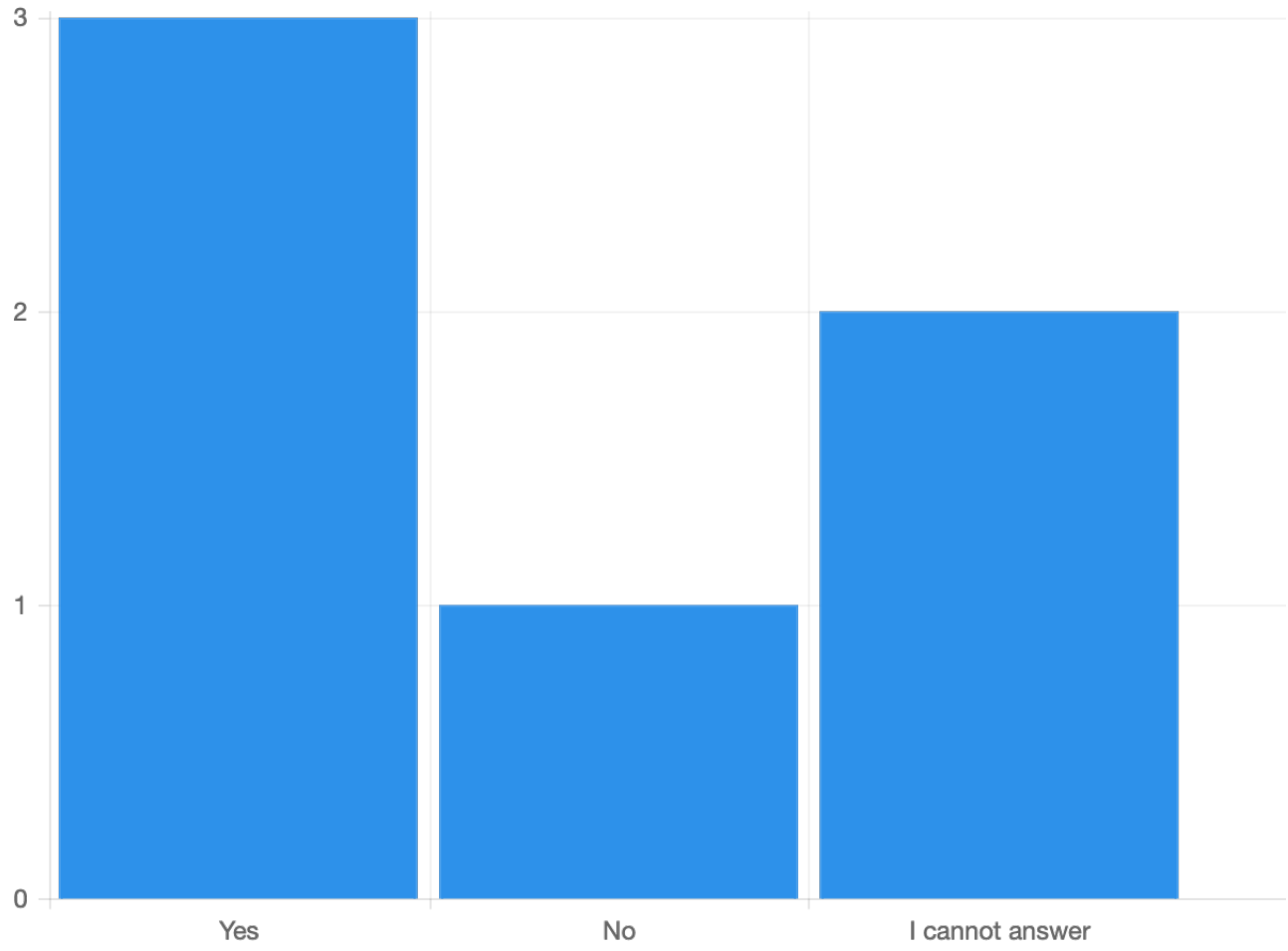
Expert 7

05/29/2024 07:37

I fully agree with Experts 1, 2, and 3 regarding data sources.

Result 3.5 *(ID: 6355)*
Question 3.5 *(ID: 5726)*

In Table 2-3, the published data of Scarselli et al. (2017) for Italian workers are proposed as a potential surrogate for U.S. worker exposures. Do you consider this use of the data appropriate. Please explain your answer.



Legend

answers: 6
skips: 1

Answer Explanations

Expert 6 Explanation
Selected Answer(s): I cannot answer

The Scarselli et al. 2017 data is certainly and good effort to summarize the exposure levels employers have to report in Italy. The job categories for the obvious BD exposure, levels seems to be similar to previous reports. However, looking at the various job categories its becomes clear that environmental BD exposures (traffic, city) are included. Most troublesome are job categories with low mean BD exposures and the high percentage of samples below LOD which was set to 1/2 LOD reported. Further method of sampling (personnel vs environmental) is missing (98%).

In my opinion we may use selected
job categories as additional evidence for exposure range and regroup other together.

Expert 5 Explanation
Selected Answer(s): Yes

The Scarselli et al. (2017) dataset is impressive and seems to be well put together, analyzed and described. The dataset provides an overall picture of the occupational exposures to BD in Italy. However, there are limitations regarding their use by TSCA as compared to the SBR worker dataset, as follows: exposure measurements were the responsibility of the business owners, so protocols were different across industries/occupations resulting in uneven data collection for industrial sectors, firm sizes and occupational groups; selection bias may have occurred as some firms may not have reported higher exposure levels; exposures in Italy may not be comparable to those in the United States due to different regulations and practices; and, the Scarselli et al. (2017) dataset contains exposure data only and does not contain health effects information on the workers. Having said that, the Scarselli et al. (2017) dataset represents many more occupational groups and activity sectors than the other data presented in Section 2 of the Round 3 Summary Report. Their data could be used to supplement the analyses of the SBR workers, but not replace the use of data in Tables 2-1, 2-2, and 2-3.

Expert 7 Explanation
Selected Answer(s): I cannot answer

I believe the data from Scarselli et al (2017) are found in Table 2-4. I looked over the published paper - However, I am not an epidemiologist or exposure scientist, so I will leave it to those with expertise in that field to determine whether or not these data can be specifically applied to occupational exposures to BD (especially in light of the named co-exposure to benzene, etc.

Expert 2 Explanation
Selected Answer(s): No

I reviewed the Scarselli et al (2017) publication . The authors reported that exposure to BD occurs in a wide - variety of activity sectors and occupational workers. The statistical analysis suggested a higher risk in the manufacture of refined petroleum products and the production of electrical energy sactors The statistical models applied in the study allow the identification of activities and occupations with different risks of 1,3- BD exposure but the exposure may not be homogeneous within and among sectors and groups. Furthermore, concurrent exposures to benzene, acrylonitrile and ethylene dichloride have been detected (known/ likely to be human carcinogens) which could compromize the BD exposure estimations and thus, quanitative cancer risk evalauations.

Expert 1 Explanation
Selected Answer(s): Yes

manufacturing process tend to be standardized and any measurements in similar operations, esp. in the first world countries, are informative.

Expert 3 Explanation
Selected Answer(s): Yes

There is a general concurrence with the US worker data. Assuming that the Italian equivalent of OSHA is approximately equivalent in protecting Italian workers, the concentrations could be accepted as representative.

Comments (4)

SCORE **Expert 2** *05/20/2024 19:22*

2 I agree with the comments of Expert 5 that the Scarselli et al (2017) data could be used to supplement the analysis of the SBR workers cohort but not replace the use of data peresented in Tables 2.1, 2.2 and 2.3. The Scarselli et al (2017) publication lists concurret exposures to benzene, acrylonitrile and ethylene dichloride and would be difficult to entangle given these chemicals are known / likely human carcinogens.

SCORE **Expert 3** *05/27/2024 04:18*

1 I agree that any concurrent chemical exposures will need to be teased out by the exposure assessor(s). I believe there is concurrence among this panel members on this point.

SCORE **Expert 7** *05/29/2024 07:40*

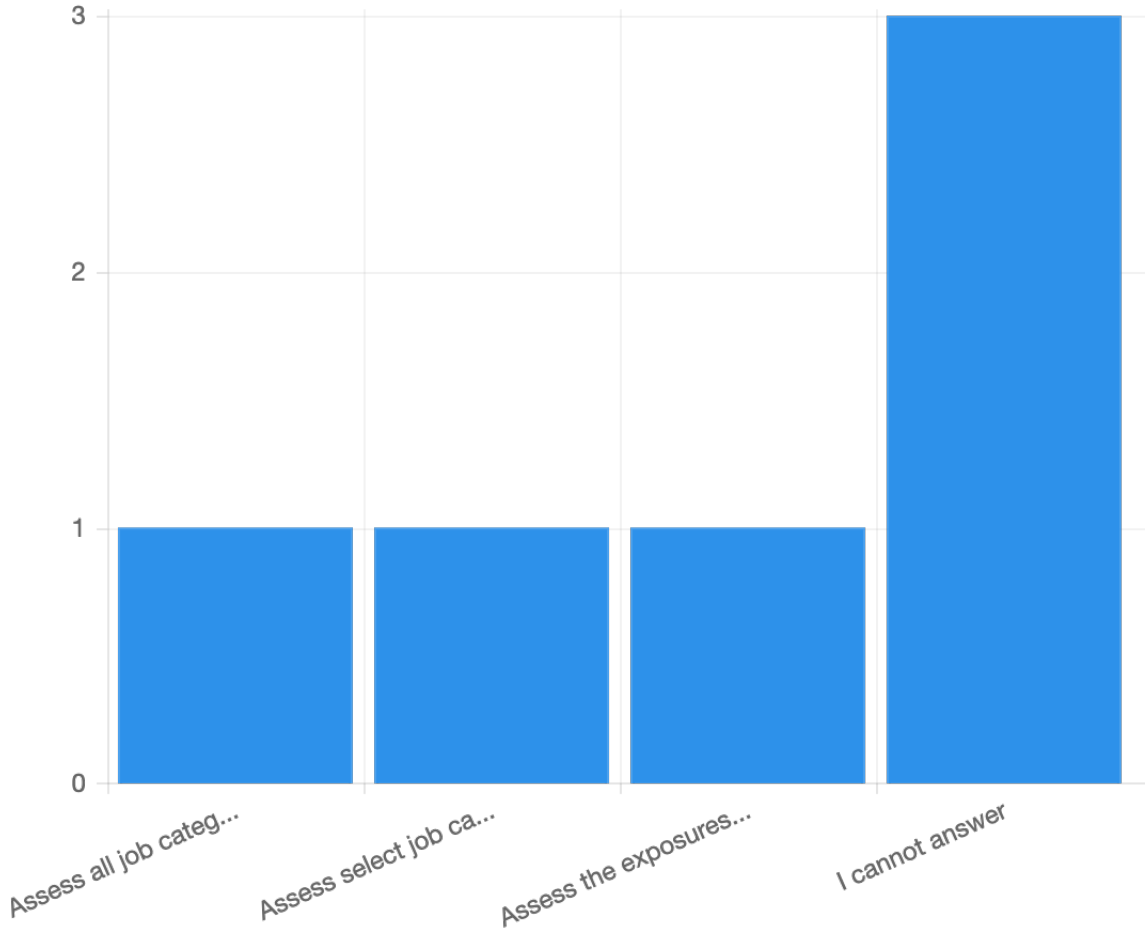
1 I agree with Experts 2 and 3 - the data from Scarselli et al (2017) should be used, as appropriate, after adjusting for (not sure if that is the right epidemiological term) those important confounding exposures....

SCORE **Expert 6** *05/31/2024 05:16*

0 I am surprised that nobody seem to have a concern about the low BD exposure groups, where levels are (1) overestimated due to high percent being below the LOD and (2) the lack of information regarding personnel vs environmental sampling.

Result 3.6 *(ID: 6356)*
Question 3.6 *(ID: 5727)*

If you consider the use of Scarselli et al. data appropriate, how should the data be used in the risk assessment?



Legend

Assess all job categories separately: 1
Assess select job categories (please indicate which ones): 1
Assess the exposures as a group (e.g., “Other workers exposed to BD”) using the combined statistics: 1
I cannot answer: 3

answers: 6
skips: 1

Answer Explanations

Expert 6 Explanation
Selected Answer(s): Assess select job categories (please indicate which ones)

I think we should select job categories with AM>0.05 and group the others with AM <0.05 together.

Expert 5 Explanation
Selected Answer(s): Assess all job categories separately

Because the Scarselli et al. (2017) dataset represents many more occupational groups and activity sectors than the other data presented in Section 2 of the Round 3 Summary Report, their data could be used to supplement the analyses of the SBR workers, but not replace the use of data in Tables 2-1, 2-2, and 2-3. The job categories should be assessed individually and not as a collective group as that would provide improved information for affected workers and industrial organizations.

Expert 7 Explanation
Selected Answer(s): I cannot answer

Again, I am not able to express a toxicological opinion on this (not an epidemiologist or exposure scientist) but it would seem to me that assessing all job categories separately would make sense.

Expert 2 Explanation
Selected Answer(s): I cannot answer

Pleas see comment answer in Question 3.5.

Expert 1 Explanation
Selected Answer(s): I cannot answer

need to read the original paper and decide. the table does not tell me all that much about how to use these data.

Expert 3 Explanation
Selected Answer(s):
Assess the exposures as a group (e.g., "Other workers exposed to BD") using the combined statistics

There are too many individual job categories and inclusion as such would result in an overly complicated (and not necessarily helpful to regulators) assessment. Worker exposure is the most important category in the overall risk assessment, so some weighting of the Italian concentration data to arrive at a single concentration for workers would be important.

Comments (6)

SCORE 2 **Expert 2** *05/20/2024 19:29*

I agree with the comments of Expert 5 and support the recommendation with a caveat that the Scarselli data could be be used to supplement the analyses of SBR workers.

SCORE 0 **Expert 5** *05/23/2024 05:57*

I like Expert #6's idea that there could be a cutoff value for exposures that eliminates job categories that are too low. Perhaps some calculations could be done to eliminate those job categories for which the means of the exposures are not statically different from zero. Having said that, it may be important to qualitatively list/discuss those job categories that are eliminated to show "for the record" that the exposures were very low.

SCORE
0

Expert 1

05/23/2024 07:45

Use of cutoffs when there is measurement error in exposure (as there sure is here) is perilous. Worth considering but with extreme caution and with full awareness that forcing a cutoff can create more problems than it solves. I avoid cutting up continuous variables in my work as much as possible.

SCORE
2

Expert 3

05/27/2024 04:27

As I have mentioned (or implied) previously, there is a tendency at EPA to needlessly complicate their risk assessments. I cynically believe that some of this can be attributed to a notion that more complicated (more like black box magic) assessments are necessarily more “scientific”. I agree with expert 6’s notion of separating the categories in a simple manner but would add that a sensitivity test should be done to affirm this choice. Second and third significant figures in an exposure assessment are very often a waste of time and resources. I also agree with expert 1’s point about cutoffs. Here again, it is easy to demonstrate the effect that the cutoffs may have on the bottom line.

SCORE
0

Expert 7

05/29/2024 07:47

I think assessing as many "job categories" as possible would provide an informative and complete human health risk assessment. However, I still respect the opinions of the Experts that have expertise in epidemiological studies - I will, therefore, leave the answer(s) to this charge question in their capable hands.

SCORE
0

Expert 6

05/31/2024 05:19

We may want to use category levels to support other exposure data.

Result 3.7 *(ID: 6357)*
Question 3.7 *(ID: 5728)*

In Section 2.2, several data sources are proposed for characterizing inhalation rates to potentially be used to calculate breathing rate ratios (BR). Please indicate if you feel there are other data sources that should be considered. Also, please indicate if any of the data sets you identify should supersede those proposed, or used as supporting data.

Expert 6

> I cannot comment on this.

Expert 5

> I have very limited experience with exposure modeling and related datasets, therefore, I have no data sources to propose beyond what is presented in the Round 3 Summary Report.

Expert 7

> Based on what I know about exposure estimation, the 2011 EFH (as referenced in Section 2.2) is a reliable and oft-referenced source of exposure inputs. I looked at the US EPA site for the EFH and while some of the chapters from the 2011 document have been updated, the chapter concerning BR is still seems to be both very valid and useful for human health risk assessment purposes (i.e. exposure assessment). The CD ATSDR also uses the 2011 EPA EFH for their inhalation values: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.atsdr.cdc.gov/pha-guidance/resources/ATSDR-EDG-Inhalation-508.pdf

Expert 2

> **I agree with the data sources identified in Section 2.2 are appropriate for characterizing inhalation rates and could be poentially used to calculate breathing rate ratios (BR) as clearly presented in Equation 4 for different Job Groups of populations (occupational workers. general adult male and female as a function of age, pregnant women,etc.) based on their activity patterns and exposure times spent indoors and outdoors. In my opinion, this is a critical step in exposure risk characterization to accurately estimate exposure to BD and have serious implications to dose - response (biological) analysis for quantitative noncancer as well as cancer risk assessments.**

Expert 1

> not my area, sorry.

Expert 3

> I do not believe that individual breathing rates are necessary for a chronic (lifetime) dose assessment for this risk assessment. Every individual over a lifetime experiences a huge variety of breathing rates. One default value would be sufficient. The differences between the various age/sex/situational groups is not big enough to affect the ultimately calculated margin of exposure in the first significant figure. If this were an academic exercise, I might agree that more scenarios, requiring breathing rate ratios, could be explored.

Comments (3)

SCORE 0

Expert 3

05/27/2024 04:30

The sources are appropriate. It is up to the assessor(s) to choose the correct model values in order to provide parameters specific to the goals of the overall risk assessment.

SCORE 0

Expert 2

05/28/2024 19:27

I agree with the data sources identified in Section 2.2 are appropriate for characterizing inhalation rates and could be poentially used to calculate breathing rate ratios (BR) as clearly presented in Equation 4. I am not aware of any data set that could supersede than prposed.

SCORE 0

Expert 7

05/29/2024 07:51

I still think that the use of the inhalation rate defaults in the EPA EFH are the most appropriate to use since they are widekly used and if this risk assessment goes to the EPA, I really believe they would look for the use of the EFH values (unless there was a scientific justification for use other another value(s)).

Result 3.8 *(ID: 6358)*
Question 3.8 *(ID: 5729)*

In Sections 2.3 and 2.4, several data sources are proposed for characterizing exposure times, frequencies, and durations. Please indicate if you feel there are other data sources that should be considered. Also, please indicate if any of the data sets you identify should supersede those proposed, or used as supporting data.

Expert 6

> Defer to others.

Expert 5

> I have very limited experience with exposure modeling and related datasets, therefore, I have no data sources to propose beyond what is presented in the Round 3 Summary Report.

Expert 7

> I did not see a section 2.4. But the data sources for characterizing these named parameters in Section 2.3 (Valdez-Flores and EPA EFH) seem to be very appropriate, in my opinion (none of the relevant exposure factor chapters of the 2011 EFH have been updated - so the 2011 values are still used and relevant).

Expert 2

> **The data sources as proposed in Sections 2.3 and 2.4 for characterizing the nature and magnitude of exposure (times, ferquencies and duration) are corrctly identified. I am not aware of any other published data sources to suprsede than as proposed , or that may be used as supporting data..**

Expert 1

> the approach seems reasonable, but I have never done similar calculations, so may not see some flaws. You may wish to specify distributional assumptions for "ranges" (uniform, triangular, something else?)

Expert 3

> These are fairly standard and can be used as is.

Comments (3)

SCORE **Expert 3** *05/27/2024 04:31*
0
I have no additional comments on this point.

SCORE **Expert 2** *05/28/2024 19:30*
0
The data sources as proposed in Sections 2.3 and 2.4 for characterizing the nature and magnitude of exposure (times, ferquencies and duration) are corrctly identified. I am not aware

of any other published data sources to suprsede than as proposed , or that may be used as supporting data..

SCORE
0

Expert 7

05/29/2024 07:52

I agree with Expert 2.

Result 3.9 *(ID: 6359)*
Question 3.9 *(ID: 5730)*

Please indicate below any additional issues related to BD exposure that you would like your fellow panelists to consider.

Expert 6

We may want to consider something like POD above environmental background in cities, in-vehicle and workplaces.

Expert 5

Expert 7

None at this time.

Expert 2

I believe that 1,3 - BD exposure risk characterization (nature, magnitude, times ,duration and frequency ,etc;) under different sets of exposure scinarios to human receptors (occupational workers, general and suceptible populations, etc;) is one of the most important and critical step in evalation of quantitative risk estimations. It must be clarerly presented in a transparent manner based on published data and application of scientifically accepted/ validated modelling approaches. I would also urge for identification , description of all uncertainties and sensitivity analysis of exposure data , when used in quantitative health risk assessment of 1, 3- BD.

Expert 1

between and within person variance in exposure at work and in general environment.

use arithmetic mean for chronic toxicity, not median/geometric mean.

Expert 3

Without going too in depth, I can see that the air concentrations of BD range at approximately 100 ppb for a worker, 10 ppb for vehicle air, and about 0.1 ppb for ambient air. In the most practical sense (see below), this means that anyone not working with or in proximity to BD would not reach a dose that is even in the lowest quartile of the cancer epidemiology study that will form the basis of this assessment. Smokers must be considered somehow, but it is beyond me how to tease BD out of the morass of toxins that smokers are exposed to.

Back of envelope calculations: Worker: 8 hours at 100 ppb, 2 hours at 10 ppb, 14 hours at 0.1 ppb = 821 ppb-hr dose, non worker: 2 hours at 10 ppb, 22 hours at 0.1 ppb = 22 ppb-hr. Non-workers are dosed at 1/40th the level that workers are. I also imagine that non-BD workers are 99% of the population.

Comments (6)

SCORE 0 **Expert 2** *05/22/2024 08:26*

None.

SCORE 0 **Expert 5** *05/23/2024 06:34*

I found Expert #6's comment about considering a POD above environmental background levels to be intriguing, but I am not sure I understand its implications, and I wondered if Expert #6 could elaborate on this idea. For example, if an environmental background level, such as a BD background exposure level in a given city, is higher than the POD from the SBR worker data, what do we do with that information? Should the MOE calculation be somehow adjusted based on this information? From a cumulative risk point of view, the city residents might then be considered as a "differentially exposed" population, so that additional exposures from a BD industrial source would increase their potential for adverse health effects. The same logic, then, would apply to smokers and people who drive for a living. More thoughts on this from Expert #6 and other panel members would be appreciated.

SCORE 0 **Expert 1** *05/24/2024 08:12*

With respect to comments of experts #5 and #6, my perhaps simplistic view is that risk per unit of exposure of BD will be the same at all levels, certainly at all "low" levels before saturation effects kick in at extreme/high doses. Thus, the relative risk for to BD will be the same in smokers and polluted cities but absolute risk would depend on total exposure. So, do we permit less exposure to BD from work among smokers and dwellers of so polluted areas? Do not think that there are such precedents in occupational exposure limits, where prevalence of smokers in a given workforce affects OEL. Interesting to think about and wonder what others on the panel make of this issue.

SCORE 1 **Expert 3** *05/27/2024 04:38*

There are a number of "academic" points that have been raised in our debate to this point. EPA will have to decide how much time and effort should be employed in chasing down precision for this assessment. Experts 2 and 5 have made good points. Expert1's debate comment raises a practical issue for EPA's assessors.

SCORE 0 **Expert 7** *05/29/2024 07:56*

I still like Expert 2's original comment.

SCORE
0

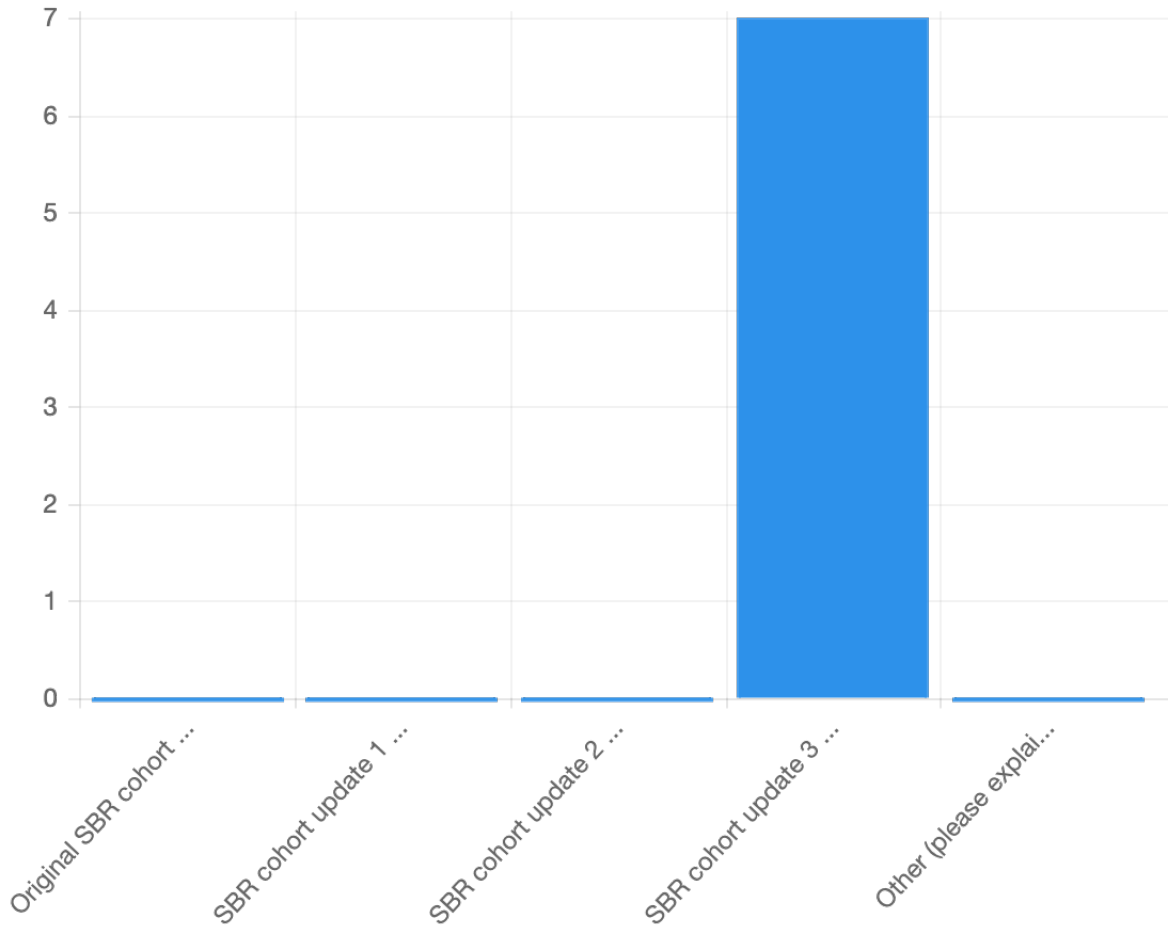
Expert 6

05/31/2024 05:28

Exp #5 What I meant was is to consider the environmental exposure for each geographical region category (city, farm, forrest). So as general population risk for living in this types of regions and then determine whether occupational exposure is higher.

Result 4.1 *(ID: 6360)*
Question 4.1 *(ID: 5731)*

Based upon input received from the panel during Round 1, there is a clear preference for relying on epidemiology data to support the calculation of an inhalation unit risk value. Which data sets should be used to support this calculation?



Legend

Original SBR cohort (Delzell, 1995; as used in USEPA 2002): 0
SBR cohort update 1 (Sathiakumar and Delzell, 2009; as used in TCEQ 2008): 0
SBR cohort update 2 (Sathiakumar and Delzell, 2009; as used in Sielken and Valdez-Flores, 2015): 0
SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022): 7
Other (please explain): 0

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation
Selected Answer(s):
SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)

Unless there is a pressing contraindication, the most recent and most expansive data set should be used. As noted in round 1, Valdez-Flores et al (2022) **seems a reasonable approach.**

Expert 6 Explanation
Selected Answer(s):
SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)

I think the most current update clearly describes the cohort and CR outcome.

Expert 5 Explanation
Selected Answer(s):
SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)

It makes sense to use the SBR cohort update 3, which is the most recent dataset, updated in 2019 (Sathiakumar et al., 2021a,b). It includes both male and female workers, improved BD exposure estimates for each individual, information on non-exposure and exposure variables that may be related to the endpoints, and more outcome data in the form of additional deaths among the workers. Although the research results presented in Valdez-Flores et al., 2022 appear to be solid, scientists in the TSCA program will want to obtain the raw data and do their own analysis of them to develop an inhalation unit risk (risk per µg/m3 air breathed) for BD. Valdez-Flores et al. (2022) highlight the importance of covariates such as age (already incorporated into the model), sex, cumulative number of BD Hits and cumulative number of styrene HITs (Tables 5 and 6). Because these covariates show a pattern of being statistically significant, they should be considered for inclusion in the final models used by TSCA.

Expert 7 Explanation
Selected Answer(s):
SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)

Agreed: the use of appropriate epidemiology data for the derivation of a inhalation (cancer) unit risk value for BD is preferred. In looking at the SBR Cohort Update 3 (as in the Valdes-Flores paper of 2022) it seems that the use of the Cox proportional hazards model is a "better way" to develop exposure-response models. Again, I am not an epidemiologist - I will have to leave the answer to this question to those experts.

Expert 2 Explanation
Selected Answer(s):
SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)

I agree with other members of the Panel that the epideniologacal data to support the calculation of an inhalation unit risk for cancers in humans for BD exposure. The original SBR cohort and it's recent updates with exposure history that could be used to develop exposure -response analysis/ models as published by Voldez- Flores et al (2022).

Expert 1 Explanation
Selected Answer(s):
SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)

it is hard for me to advise: the most recent update by the original authors seems like the best starting point.

Expert 3 Explanation

Selected Answer(s):

SBR cohort update 3 (Sathiakumar et al., 2021a,b; as used in Valdez-Flores et al., 2022)

The most recent data have been collected and analyzed using the most modern models, resulting in fewer (precautionary) assumptions.

Comments (4)

SCORE 2 **Expert 2** *05/20/2024 19:45*

I don't see any disagreement based on comments of experts that the original cohort and its recent updates of epidemiological data (Voldez et al (2022) is the most appropriate to calculate the inhalation cancer unit risk value.

SCORE 0 **Expert 1** *05/22/2024 07:58*

I agree with expert 1 on this, unless the most recent papers are more flawed than the older ones. One would have to compare them carefully in terms of risk of bias. But if all is done by the same team, then the most recent update is the right one.

SCORE 0 **Expert 3** *05/27/2024 04:39*

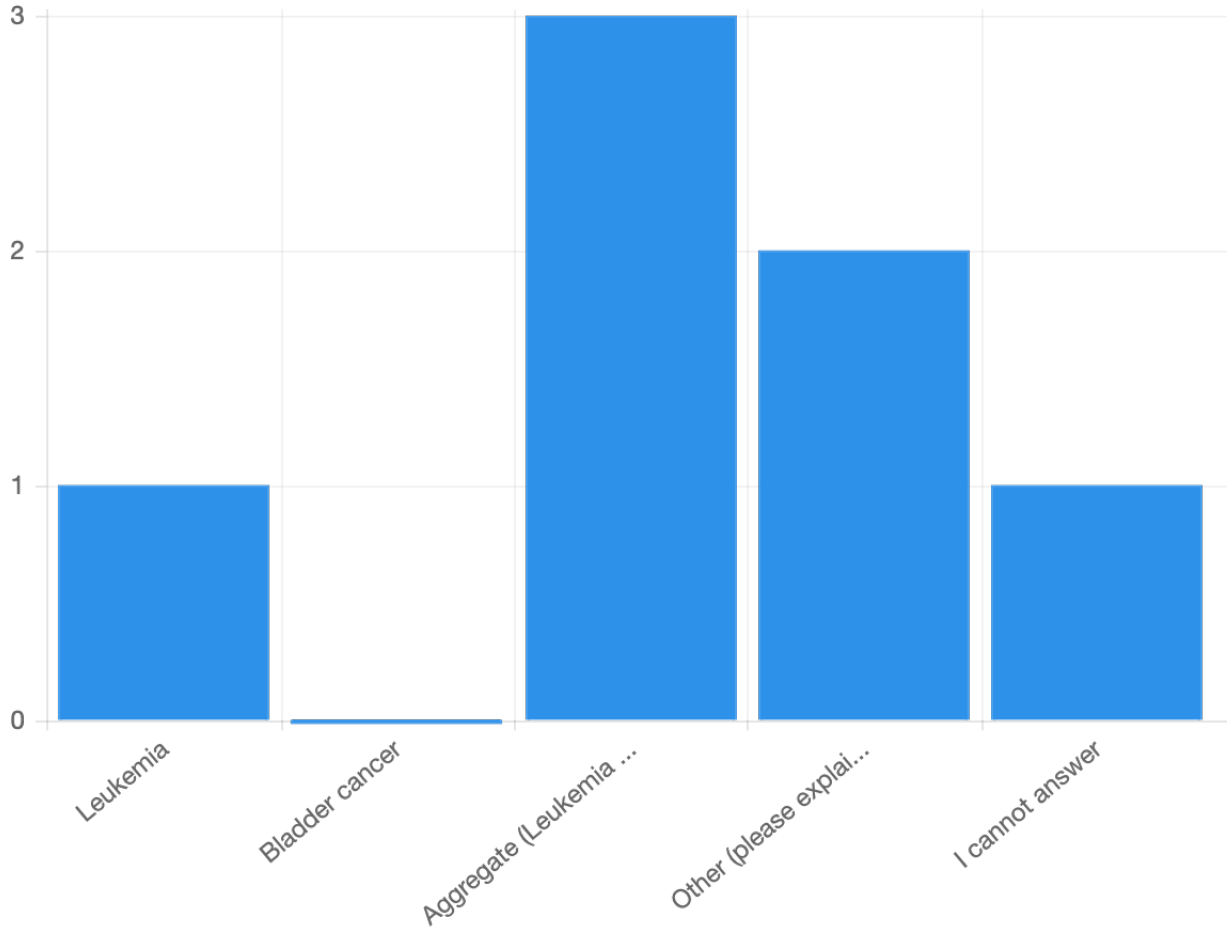
No additional comment.

SCORE 1 **Expert 7** *05/29/2024 07:57*

It seems that all Experts are in agreement with what data sets should be used.

Result 4.2 *(ID: 6361)*
Question 4.2 *(ID: 5732)*

Using the epidemiology data, what endpoint(s) should be used to calculate the inhalation unit risk?



Legend

Leukemia: 1
Bladder cancer: 0
Aggregate (Leukemia + Bladder cancer): 3
Other (please explain): 2
I cannot answer: 1

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation
Selected Answer(s): Aggregate (Leukemia + Bladder cancer)

The inclusion of both tumor sites makes more use of available relevant data. As noted below in 4.3 the resulting unit risks are not that different for the separate and combined data sets.

I generally prefer presenting the plausible alternatives, (as in summary table 3.3) and noting the pros and cons underlying a choice (or choices).

Expert 6 Explanation
Selected Answer(s): Other (please explain)

We should consider Leukemia and Bladder cancer each individually and together.

Expert 5 Explanation
Selected Answer(s): Other (please explain)

The exposure-response modeling of mortality from BD exposures should be done on leukemia alone (positive exposure-response in Sathiakumar et al., 2021a) bladder cancer alone (positive exposure-response in Sathiakumar et al. 2021b) and an aggregate of leukemia and bladder cancer together, and the results compared. The most appropriate inhalation unit risk can then be chosen based on criteria such as model fit statistics, the robustness of the underlying data, or simply, by choosing the most conservative value for human health protection. As shown in Valdez-Flores et al., 2022, covariates should be investigated within the modeling process, including age (already incorporated into the model), sex, cumulative number of BD Hits and cumulative number of styrene HITs.

Expert 7 Explanation
Selected Answer(s): Leukemia

Again, in my "research" as a non-epidemiologist, it seems to me that there is a relationship (2X or so) between co-occupational exposure to BD and styrene but the relationship between each individual monomer and bladder cancer risk can't be determined. However, it also seems to me that there is a much stronger relationship between exposure to BD and production of leukemia (i.e. Valdez-Flores and papers within). So, my initial answer is to focus on just leukemia since the study is focused on cancer and BD exposure.

Expert 2 Explanation
Selected Answer(s): Aggregate (Leukemia + Bladder cancer)

Based on my review and I believe that the publication of Voldez- Flores et al includes the most recent update of male and female workers of the SBR study with a follow-up through 2009 (2009 Sethikumar et al) is the best available comprehensive approach considering an aggregate response (all leukemia, myeloid leukemia, multiple myeloma, nonNHL, and bladder/urinary cancer) with characterization of total risk cancer risk to humans from exposure to 1,3- BD and it shoud be used in evaluation and calculation for derivation of the estimated inhalation unit risk for occupational and environmental exposures to 1,3- BD.

Expert 1 Explanation
Selected Answer(s): Aggregate (Leukemia + Bladder cancer)

both are suspected as being due to BD

Comments (4)

SCORE 1 **Expert 1** *05/22/2024 08:00*

I think we agree that both endpoints should be used. However, it would an error to combine the two outcomes as expert 6 seems to suggest. The two diseases have different pathologies,

and one only increases outcome misclassification by combing the two by simple addition. But perhaps I misundestood.

SCORE 1 **Expert 2** *05/28/2024 19:43*

I think both the cancer endpoints (leukemia and bladder cancer) should be used to calculate the inhalation unit risk of BD exposure using the published epidemiological data.

SCORE 2 **Expert 7** *05/29/2024 08:05*

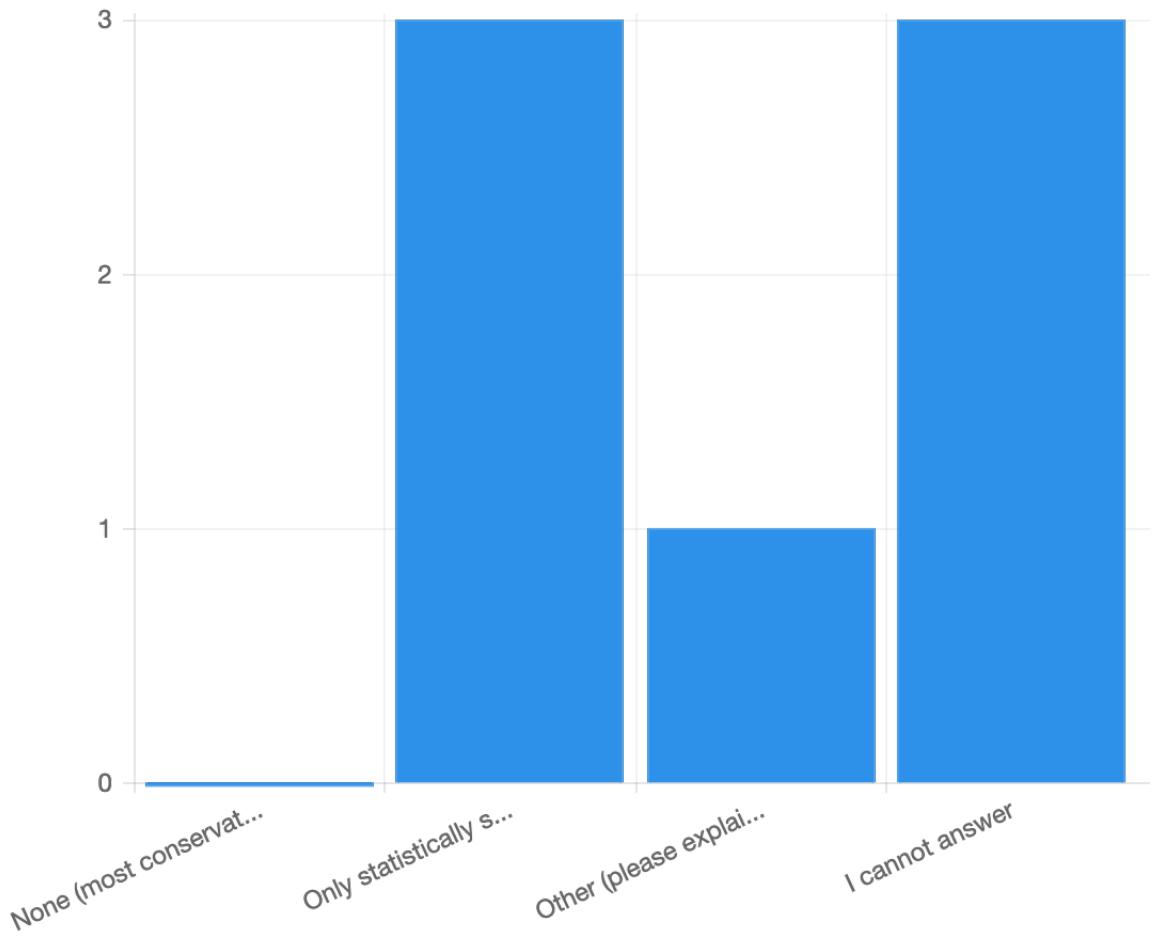
Not to get too much more complicated, but could the risk assessment use bladder cancer and leukemia individually and then also do them in combination? This could go a long way in answering any health-related questions from EPA (and others) "down the road".

SCORE 0 **Expert 6** *05/31/2024 05:32*

Wide agreement on doing the risk assessment for both.

Result 4.3 *(ID: 6362)*
Question 4.3 *(ID: 5733)*

Within the Cox proportional hazards modeling (e.g., Valdez-Flores et al. 2022), what covariates should be included in the regression model used to calculate the inhalation unit risk?



Legend

None (most conservative since all cancer response attributed to cumulative BD exposure): 0
Only statistically significant covariates (e.g., BD high intensity tasks or HITS, Sex; less conservative since some of the cancer response is attributed to these factors): 3
Other (please explain): 1
I cannot answer: 3

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation
Selected Answer(s):

Only statistically significant covariates (e.g., BD high intensity tasks or HITS, Sex; less conservative since some of the cancer response is attributed to these factors)

Generally speaking the correction for covariates is preferred as one is trying to tease out the degree to which the

observed effect is a consequence of the exposure of interest. Note that the final calculated unit risks in summary table 3-3 are within a factor of 3.5. My preference would be for the leukemia / urinary tract tumor site data with consideration of statistically significant covariates, as likely to be the more precise measurement of a butadiene exposure effect. (But the end results of all the permutations don't vary widely).

Expert 5 Explanation

Selected Answer(s):

Only statistically significant covariates (e.g., BD high intensity tasks or HITS, Sex; less conservative since some of the cancer response is attributed to these factors)

Only statistically significant covariates should be included, such as BD high intensity tasks (HITS), styrene exposures, and sex (age is controlled for by the structure of the Cox proportional hazards model). The goal of the exposure-response analysis should be to develop the most accurate representation of the BD exposure-response relationship. After examining the characteristics and quality of the study data and the results of the exposure-response modeling, conservative adjustments can be applied to the modeling results as informed by data or as decided upon based on health protective policies, if deemed appropriate. Such conservative adjustments should be explained in detail in the final TSCA report.

Expert 7 Explanation

Selected Answer(s): I cannot answer

Out of my expertise - leave this to the experts in epidemiology.

Expert 2 Explanation

Selected Answer(s):

Only statistically significant covariates (e.g., BD high intensity tasks or HITS, Sex; less conservative since some of the cancer response is attributed to these factors)

I think both, non-exposure such as age of the subject individual workers, gender, race/ethnicity, years since hire and exposure (cumulative ppm -years) varibles for high and low intesity tasks should be used in developing exposure metrics. It is important to have an access to exposure and history for each individual worker to estimate exposure to fit the Cox proportional model for the cancer endpoints in questiion.

Expert 1 Explanation

Selected Answer(s): Other (please explain)

never use p-values to select covaries: option 2 is wrong.

option 1 is wrong because it is most vulnerable to confounding.

develop and DAG and force all variables prescribed by DAG to get adjusted HR.

Covariate adjustment in Valdez-Flores et al. 2022 seems to make a big difference and I would need to understand why before using the result for any purpose. Seems like a very non-standard paper, so I am hesitant to just trust the calculations it reports. Proportional hazard assumption is not mentioned and may not have been tested. These are red flags for me, signaling that there may be something importantly wrong with the analysis.

Comments (7)

SCORE 1

SciPinion Admin

05/20/2024 14:48

Clarification from the Risk Assessment Team: *In response to Expert 1, the risk assessors would like to offer the following points of clarification:*

First, we would like to make a clear distinction between "predictive" statistical models and "causal or explanatory" statistical models, which is well-discussed by Shmueli (2010; https://projecteuclid.org/journals/statistical-science/volume-25/issue-3/To-Explain-or-to-Predict/10.1214/10-STS330.full).

For developing a predictive model, covariate selection focuses on improving model predictions while also limiting overfitting (i.e., overly complex/non-parsimonious model that yields predictions that are too specific to a particular dataset, reducing its generalizability). The assessment of Valdez-Flores et al. (2022) falls into this category of statistical model (i.e. to answer the question, what is the risk of cancer given a BD exposure of X?). Although there are currently no specific guidelines from USEPA regarding how decisions in epidemiology-based assessment such as covariate selection should be conducted (something that is sorely needed given the lack of consistency across epidemiology-based assessments within EPA's IRIS database), TCEQ (2015; https://www.tceq.texas.gov/downloads/toxicology/publications/rg-442.pdf) has provided guidelines that address this topic (see Section 7.7.10 Covariate Effects). The assessment of Valdez-Flores et al. (2022) was conducted in a manner consistent with TCEQ guidelines (note - this consistency is not unexpected as Dr. Valdez-Flores was a contributing author to the guidelines).

On the other hand, for developing causal/explanatory statistical model, the independent variables are regarded as causes of the dependent variable, and the goal is to determine whether & extent covariates affect the dependent variable (i.e, to answer the question, what would happen to an outcome as a result of treatment or intervention). Such models are often more complex than predictive models and can include tools such as directed acyclic graphs (DAG) as suggested Expert 1. We are not aware of DAG being applied to the derivation of a cancer unit risk value by EPA or by other agencies/risk assessors. While this would be an interesting exercise, it would require extensive methods development and efforts that are outside of the current scope for this project.

SCORE 0

SciPinion Admin

05/20/2024 14:49

Clarification from the Risk Assessment Team: *Regarding the other comment raised by Expert 1 about the assumption of proportional hazards, we can quote Paul D. Allison book "Survival Analysis Using SAS: A Practical Guide", Second Edition, 2010. SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513.*

The proportional hazards model assumes that "the hazard for any individual is a fixed proportion of the hazard for any other individual." The "fixed proportion" means that the proportion does not change with time. However, "whenever you introduce time-dependent covariates into a Cox regression, it is no longer accurate to call it a proportional hazards (PH) model. Why? Because the time-dependent covariates will change at different rates for different individuals, so the ratios of their hazards cannot remain constant." For BD, cumulative BD

exposure and cumulative number of BD HITs are time-dependent covariates in the model.The partial likelihood of the Cox PHM can still be used.

Allison goes on to say:

"But suppose you don't have any time-dependent covariates. How do you know whether your data satisfy the PH assumption, and what happens if the assumption is violated? Although these are legitimate questions, I personally believe that concern about the PH assumption is often excessive. Every model embodies many assumptions, some more questionable or consequential than others. The reason people focus so much attention on the PH assumption is that the model is named for that property. At the same time, they often ignore such critical questions as: Are all the relevant covariates included? Is the censoring mechanism noninformative? Is measurement error in the covariates acceptably low? As in ordinary linear regression, measurement error in the covariates tends to attenuate coefficients (Nakamura, 1992).

To put this issue in perspective, you need to understand that violations of the PH assumption are equivalent to interactions between one or more covariates and time. That is, the PH model assumes that the effect of each covariate is the same at all points in time. If the effect of a variable varies with time, the PH assumption is violated for that variable. It's unlikely that the PH assumption is ever exactly satisfied, but that's true of nearly all statistical assumptions. If we estimate a PH model when the assumption is violated for some variable (thereby suppressing the interaction), then the coefficient that we estimate for that variable is a sort of average effect over the range of times observed in the data. Is this so terrible? In fact, researchers suppress interactions all the time when they estimate regression models. In models with even a moderately large number of variables, no one tests for all the possible 2-way interactions— there are just too many of them."

SCORE
0

Expert 1

05/22/2024 08:09

I understand the difference between predictive and causal models and what PH assumption is, but it is good to have a high-level synopsis from the RA Team. The point is that the calculations of Valdez-Flores et al. 2022 fall far below the standard that I accept in my own work and as editor.

DAGs or causal thinking is needed for both types of models. The dichotomy you are arguing is false, because research question always informs model structure, whether aims are predictive or causal. A good model typically is fit for both purposes but in epidemiology the aim is ALWAYS to derive a causal model.

PH assumption is trival to test, so there is no excuse for not doing it, especially for policy-rerevant analysis.

If there appear too many plausible interactions, there are special statistical methods to deal with this. Pretending the interactions do not exist is the worst choice, as it invalidates causal interpretation all

main effect estimates.

SCORE 0

Expert 5

05/23/2024 15:10

I agree with Expert #1 that the development of a DAG could be useful to identify important variables and their roles in leading to the health outcome, e.g., causal variables, confounders, effect modifiers. However, other variables may also be of interest because they were important variables in previous carcinogenic unit risk derivations or because they are relevant to the industry being assessed. Once an initial group of variables has been identified, I am OK with using statistical significance to narrow the set of variables to those that best predict the endpoint of interest and limit overfitting of the model. This practice is commonplace in conducting linear regressions, and I have no issue with using this approach in Cox proportional hazards modeling. Regarding the proportional hazards assumption, I too think it should be tested. If the assumption is met, then the results of the analysis will be robust, and the model will be predictive. If the assumption is not met, then other more appropriate models may need to be considered. Interactions among the predictor variables could certainly be of concern. For example, suppose an interaction between styrene exposures and BD high intensity tasks is suspected, then a model that allows for including and testing for this interaction would be desirable.

SCORE 0

Expert 7

05/29/2024 08:07

I am not able to make any comments one way or another - will leave it to the Experts that have already weighed-in.

SCORE 0

Expert 2

05/29/2024 13:30

I think statistically significant covariates should be included, that may include job categories of high intensity tasks , exposures to styrene,, gender, race and smoking history. T

SCORE 0

Expert 6

05/31/2024 05:36

Out of my expertise.

Result 4.4 *(ID: 6363)*
Question 4.4 *(ID: 5734)*

Please indicate below any additional issues related to BD cancer assessment based on epidemiology data that you would like your fellow panel members to consider.

Expert 4

I agree with the summary that "Rodent-based unit risk values are considered supportive of the epidemiology-based unit risk values . . ." as evaluated in Kirman and Hays (2022), but I would make more use of their analyses in a revised document.

I would include the discussion of variation among species (rat, mouse, human) that is elegantly described in Kirman and Hays (2022). This in turn would lead to the presentation of MOA. I would emphasize the role of the bifunctional alkylating metabolites in likely clastogenic effects contributing (perhaps more than point mutations) to the rodent tumors. I suggest including discussion of the genotoxic potency and specificity of the three major metabolites in the context of a MOA for the observed human neoplasms.

In addtion, I would make note of the following discussion in Kirman and Hays (2022): "In contrast, the slope term for lymphomas regression indicates that the concentration term is much more important than the exposure
duration term for the observed cancer response. This result is inconsistent with Haber's conjecture, and suggests that there may be important mechanistic differences in BD's role in producing mouse lymphomas compared to the solid tumors observed in mice." I consider it important to highlight likely differences in mechanism / MOA among the tumors associated with butadience exposure to rodents.

As corollary, I accept that low dose linear extrapolation is a suitable default in the absence of a well-established MOA for humans. But I am not convinced that this is the most data-based way to proceed in the evaluation of butadiene. I also suggest that the discussion of life stage susceptibility in Kirman and Hays (2022) be included in the cancer risk assessment. I found their arguments to be convincing that no age dependent adjustment factor (ADAF) was needed (based on cyp2E1 formation early in life, as well as the data in mice for lack of increased tumor inicdence following a single early life stage exposure).

I don't know that it helps the arguments n the summary document to refer to "NAM" regarding the rodent data unit risks. Many folks associate NAMs with in silico data. What was done in the development of the unit risks from rodent data was rather an appropriate application of contemporary methods to available data.

Expert 6

Expert 5

I would like for the panel members and EPA to consider the impacts of smoking behaviors on the BD exposure-response modeling results, even though adjusting for smoking is not a conservative approach to human health protection from BD exposures. The Round 1 summary materials showed that the NHANES biomarker data on BD was six times higher for smokers vs. nonsmokers in 2015

(Table 2), demonstrating important background BD exposures in smokers. In addition, Fircanis et al. (2014) conducted a meta-analysis of the epidemiologic literature, concluding that "cigarette smoking proves to be a significant risk factor for the development of acute myeloid leukemia (AML) in adults" (Source: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.23744). In a similar effort, Rink et al. (2015) concluded that "retrospective evidence suggests that smoking markedly increases urothelial carcinoma of the bladder (UCB) risk and may lead to unfavorable outcomes for patients who already have UCB (Source: https://www.eu-focus.europeanurology.com/article/S2405-4569(15)00009-7/abstract). These two studies show associations between smoking and both leukemia and bladder cancer, the primary endpoints of interest in the BD assessment. Valdez-Flores et al., 2022 state that their models, "were not adjusted for smoking because no data were available for this covariate", implying that smoking would likely be a statistically significant covariate if it could be included. It seems illogical not to account for smoking, and it is unclear why data on smoking behavior was not collected in this cohort and, apparently, continues to not be collected by the investigators. The assumption being made by not adjusting for smoking is that smoking behaviors are the same for all workers in the SBR cohort, likely an erroneous assumption. Without accounting for smoking behaviors, risk estimates from the BD exposure-response modeling would be biased high, with steeper slopes for models unadjusted for smoking.

It may be possible to adjust the results of exposure-response modeling to reflect in general the smoking behaviors of the SBR workers. The Round 1 summary materials presented NHANES biomarker data on BD for smokers vs. nonsmokers, implying that these data could potentially be of use in evaluating carcinogenicity and mortality risks resulting from modeling the BD exposures in this cohort. In addition, the CDC published a report in 2011 on cigarette smoking prevalence among working adults, stratified by socioeconomic variables and by industry and occupation group in the U.S. for the years 2004-2010 (Source: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6038a2.htm#tab2). For example, for manufacturing workers, age-adjusted cigarette smoking prevalence was reported to be 23.2% (95% CI=21.9%-24.5%); for production workers, it was 26.1% (95% CI=24.6%-27.7%). Such data on BD biomarkers and smoking prevalence could be used to adjust the inhalation unit risks from BD exposures to account for smoking behaviors.

Expert 7

None at this time.

Expert 2

I believe metabolism 1,3- BD is an important isuue in determination of carcinogenicity in humans given species differencs in formation of reactive electrophilic epoxy metabolites with likely different genotoxic potentcies and sensitivities to carcinogenic outcomes that may contribute to nonlinearity in dose- response relationships, Therefore , it is icritical to recognize and consider the sources of nonlinearity in quantitative human cancer risk assessment of, 3-BD. I believe that nonlinear quantiatve cancer risk assessment should be exploerd and presented along with the linaer dose -response risk asessment wich is a preferred and routinely selected choice by the US EPA and other ferderal regulatory agencies. The 2005 US EPA cancer risk assessment calls for presentation of both linear and

nonlinear approaches for cancer risk assessments of environmental agents.

Expert 1

non-linearity is the only huge elephant the room: how to fit a model that allows for thresholds and other complications that are forced out of the model by Cox PH approach.

Comments (7)

SCORE 0 **Expert 4** *05/21/2024 13:58*

I appreciate the comments of Expert 5 re smoking. I need to cogitate on this a bit more, and I look forward to reading other comments.

SCORE 1 **Expert 4** *05/21/2024 13:59*

I am happy to repeat my opinion that low dose linearity is likely not the approach most supported by the various lines of evidence.

SCORE 1 **Expert 1** *05/22/2024 08:16*

On the matter of smoking, just because it is related to exposure and outcome it does not mean that it materially affects epi analysis. There are methods dating back to 1980's that can help determine the extent of bias from latent confounding and it is certainly sensible to apply then and their more modern version here. Key reference that I turn to are:

1. Axelson O. Dealing with the exposure variable in occupational and environmental epidemiology. Scand J Soc Med. 1985;13(4):147-52.

2. Axelson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. AmJIndMed. 1988;13:105-18.

3. McCandless LC, Gustafson P, Levy AR. A sensitivity analysis using information about measured confounders yielded improved uncertainty assessments for unmeasured confounding. JClin Epidemiol. 2008;61(3):247-55.

One can also use Lash/Fox quantitative bias analysis for unmeasured confounding. Mat be trivial to perform in this case.

Note that the usual outcome of such analyses in occupational cancer epi is that smoking does not matter because all members of the cohort have very similar smoking patterns and histories. But one can never be sure that the next application will not prove to be an exception in the pattern.

SCORE **Expert 5** *05/28/2024 10:25*

2

Thank you to Expert #1 for the information showing that unmeasured smoking behaviors might not be of consequence for evaluating cancer from BD exposures in the SBR occupational work force. The quoted articles do seem to support this claim and that is good news since the SBR worker data on smoking was not collected. I have been under the impression for a long time that smoking behavior is often a very important confounding factor to be considered in epidemiology studies. I am not an epidemiologist so I must defer to others on the panel, but I do still have some concerns that I hope other panel members can address. In particular, the CDC data I have already quoted suggested that "for manufacturing workers, age-adjusted cigarette smoking prevalence was reported to be 23.2% (95% CI=21.9%-24.5%); for production workers, it was 26.1% (95% CI=24.6%-27.7%)", so apparently, approximately 75% of manufacturing and production workers do not smoke. Thus, I have trouble understanding the assumption that smoking behaviors are the same for all workers in the SBR cohort.

I also found a similar article, Kriebel et al. 2004, where they state, "When comparing exposure groups within the same working population, it is unlikely that either systematic or chance differences in smoking and drinking habits will cause as much as a 20% change in the relative risk in large studies. While this study focused on an occupational exposure and laryngeal cancer, there are many situations in which epidemiologists are concerned that unmeasured 'lifestyle factors' may differ among exposure groups, and it would appear that the likely confounding effect of such differences will often be modest." Although their conclusions offer good news, the authors seem to suggest that a "20% change in the relative risk" can be considered "modest", but 20% may be considered a significant change in relative risk from a risk assessment perspective.

Kriebel D, Zeka A, Eisen EA, Wegman DH. Quantitative evaluation of the effects of uncontrolled confounding by alcohol and tobacco in occupational cancer studies. Int J Epidemiol. 2004 Oct;33(5):1040-5. doi: 10.1093/ije/dyh151. Epub 2004 May 20. PMID: 15155700.

SCORE
0

Expert 7

05/29/2024 08:08

Again, I am not able to make any comments one way or another - will leave it to the Experts that have already weighed-in

SCORE
0

Expert 2

05/29/2024 13:36

I think it is important to consider the sources of nonlinearity in quantitative human cancer risk assessment of, 3-BD. I believe that nonlinear quantiatve cancer risk assessment should be exploerd and presented along with the linaer dose -response risk asessment which is a preferred choice by the US EPA. The 2005 US EPA cancer risk assessment calls for presentation of both linear -

and nonlinear approaches for cancer risk assessments of environmental agents

SCORE
0

Expert 6

05/31/2024 05:53

I agree with Expert #5 that when possible smoking status should be considered, since BD has been recently rated the cigarette constituent with the highest cancer risk index (Fowles and Dybing 2003).

Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tob. Control.* 2003;12:424–430

Result 5.1 *(ID: 6365)*
Question 5.2 *(ID: 5736)*

Please indicate your preference for adjusting for species differences when extrapolating fetal body weight dose-response data from rodents to humans

Horizontal bar charts are not supported in the report view.

Answer Explanations

Expert 4 Explanation

Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

The approach described in Kirman et al (2022) makes the most appropriate use of available data for scaling among species. There is sufficient documentation supporting the utility of hemoglobin adduct measurements in this scaling.

Expert 6 Explanation

Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

The haemoglobin adduct data are certainly the best set to assess internal BD exposure and any potential spices, sex or other difference in BD uptake, distribution and metabolism.

When discussing BD metabolism to the 3 epoxide metabolites, additional evidence that should be included are the free oxides in blood and urine biomarker studies, by Filser and Tretyakova groups, respectively. These data, while difficult to build into the risk assessment clearly show the metabolic differences and can support the selection of uncertainty factors based of the haemoglobin adducts.

This is a quite restricted question. It would be interesting to see how the PBPK internal doses estimates compares to the estimates based on the haemoglobin adducts.

Expert 5 Explanation

Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

Based on the information presented to this panel, it seems imperative that differences in metabolic activation be accounted for in the development of toxicity values for BD. Thus, the first three options are not appropriate for use in evaluating BD. In addition, DEB is an important contributor to toxicity, so the fourth option of internal dose based on PBPK modeling can also be excluded. From Kirman et al. 2022, for fetal body weight changes, the animal to human extrapolation factors for the kinetic portions of uncertainty (EFAKs) are 0.00563 and 0.127 for mouse to human and rat to human, respectively (Table 6), based on the combined cytotoxicity indices for the 3 metabolites in each species. These factors were used to calculate human equivalent concentrations for the mouse

and rat concentration-response data, accounting for differences across species in the internal doses of EB, DEB, and EBD, under an assumption that all three metabolites contribute to the observed changes in fetal body weight. This type of EFAK analysis should be used by TSCA to develop human equivalent concentrations for development of Reference Concentrations.

Expert 7 Explanation

Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

Based on my reading of some of the bioactivation literature of BD, it seems that of the three primary reactive BD metabolites, the reactive metabolite DEB is the most potent mutagen (i.e. from the ATSDR Toxicological Profile: "The weight of evidence strongly suggests that 1,3-butadiene metabolites, rather than 1,3-butadiene itself, are responsible for genotoxic effects, due to their highly reactive nature. Of these metabolites, the order of potency for mutagenicity is DEB >> EB > EDB."). Therefore, the logical toxicological "choice" for adjusting for species differences would be the one noted that addresses the metabolic activation of BD to DEB.

Expert 2 Explanation

Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

I prefer an approach of adjusting for species differences to extrapolating fetal body weight dose-response data from nice to humans as proposed by Kirmann et al 2022.This approach is well justifed given large species diffrences in metabolism of 1, 3- BD in mice, rats, and humans resulting in different internal doses of major reactive epoxy metabolites, presuming that they are responsible forthe observed species differences in sensitivity of BD tocicity. This approach reflects the best available science and supports the argument for application of data derived extrapolation factors to replace default uncertanty factors to account for species differences.

Expert 1 Explanation

Selected Answer(s): I cannot answer

see above

Comments (5)

SCORE 0 **Expert 4** *05/21/2024 14:04*

Taking note of Expert 7's comments, allow me to continue flogging the moribund horse of non-linearity. Even a relatively potent bifunctional alkylating agent does not necessarily produce a genotoxic or mutagenic (or certainly not a clastogenic) effect in one step.

SCORE 0 **Expert 2** *05/22/2024 08:30*

I prefer an approach of adjusting for species differences to extrapolating fetal body weight dose-response data from mice to humans as proposed by Kirmann et al 2022.This approach is well justifed given large species diffrences in metabolism of 1, 3- BD in mice, rats, and humans resulting

in different internal doses of major reactive epoxy metabolites, presuming that they are responsible for the observed species differences in sensitivity of BD toxicity. This approach reflects the best available science and supports the argument for application of data derived extrapolation factors to replace default uncertanty factors to account for species differences

SCORE
0

Expert 5

05/24/2024 08:29

Just to offer a little clarity regarding nonlinear vs. linear dose-response by EPA. In general, EPA has evaluated carcinogens using a low dose linear extrapolation based on a one hit model for cancer biology. There have been exceptions, e.g., chloroform, which is thought to be a threshold carcinogen and was evaluated using a nonlinear approach. For noncancer effects, there is in general an assumption of nonlinearity, and the POD is usually selected within the dose range of the toxicity data. The reference value is then lowered to a human safe level through the use of uncertainty factors. Thus, nonlinearity is not an issue for modeling the fetal body weight and ovarian atrophy effects of BD, but it is a debatable issue for the BD cancer assessment.

SCORE
0

Expert 7

05/29/2024 08:11

I agree with Expert 2's comment regarding the use of Kirman et al (2022) for adjusting for species differences. It seems very reasonable and is already in the published, peer-reviewed literature.

SCORE
0

Expert 4

05/29/2024 10:20

Back to my nearly dead horse.

The US EPA cancer guidelines (2005) made it clear that extrapolation below a calculated point of departure was to be informed by the mode of action of the agent being considered. Parts of EPA have been very reluctant to follow their own guidelines and have gone "all linear all the time". A notable exception has been for some plant protective agents (and a few other chemicals) when data have been sufficient to support a biologically based dose response (BBDR) model or a MOA that clearly specifies a threshold for one or more key events.

Note that for chloroform, the risk asssessors involved agreed that the MOA supported a threshold for carcinogenicity. That risk assessment was accepted by the Agency only after a lawsuit.

And a further note: if one truly applies US EPA (2005) then any extrapolation below a calculated POD should be informed by consideration of MOA for any endpoint, not only cancer. Thus a BBDR or non-threshold approach could (and maybe should) be considered for non-cancer risk assessment.

Result 5.2 *(ID: 6364)*
Question 5.1 *(ID: 5735)*

As discussed in Kirman et al. (2022), species differences are noted for fetal body weights changes as reported in mice and rats exposed to BD (Hackett et al. 1987a,b), which may be explained by species differences in metabolic activation of BD. Please indicate your preference on the species used to support toxicity values for BD human health risk assessment

Horizontal bar charts are not supported in the report view.

Answer Explanations

Expert 4 Explanation
Selected Answer(s): **Reference concentration should be based on data from both species**

Kirman et al (2022) presents calculations from both rat and mouse data sets as well as on the combined data sets. For the combined data sets, toxicokinetic (TK) differences among species can be adjusted for in the application of a human equivalent concentration for modeling. Other species-specific differences can also be accounted for: e.g. as noted in Kirman et al (2022) "The combined data set for mice and rats includes observations from 156 litters and were expressed in terms of fraction of control values to account for species differences in fetal weights in control animals (rat > mouse)."

The mode of action for fetal body weight changes (cytotoxicity) is equally applicable to mice and rats, and presumably to humans as well. Species differences then would likely be attributable to the rate and amount of bifunctional alkylating agents (DEB) and the less potent monofunctional alkylators (EBD and EB) reaching the target tissue.

Given these considerations, use of the larger combined data set seems appropriate

Expert 6 Explanation
Selected Answer(s): **Reference concentration should be based on mouse data**

Expert 5 Explanation
Selected Answer(s): **Reference concentration should be based on mouse data**

Table 3 in Kirman et al. 2022 shows the mouse and rat data for exposures to BD for fetal body weight changes. Fetal body weight changes were observed in mice at all tested concentrations, the lowest of which, 40 ppm, was also the lowest concentration administered to the rats. This effect was not observed in the rats at any of the tested concentrations, and no dose-response trend was apparent. For the development of toxicity values, studies in which significant effects are observed are preferred to those not showing effects at any dose level (i.e., the study results in a “free-standing No-Observed-Adverse-Effect-Level” at the highest concentration). Thus, the mouse data would be preferred. A toxicity value for fetal body weight changes does not need to be developed using the rat data, and the datasets should not be combined for the derivation of a Reference Concentration.

Expert 7 Explanation

Selected Answer(s): Reference concentration should be based on rat data

From the ATSDR Toxicological Profile of BD: Comparison of rat and mouse data identify large differences in sensitivity to 1,3-butadiene, which are due to metabolic differences between species. Humans, rats, and mice metabolize 1,3-butadiene using the same enzymatic pathways resulting in the production of the same reactive metabolites, in particular, EB, DEB, and EBD. However, quantitative differences in the rate of formation and detoxification of reactive metabolites have been found that result in higher tissue levels of reactive metabolites in rodents, particularly mice, than in humans (Bond et al. 1993; Csanády et al. 1992; Dahl et al. 1991; Filser et al. 2001, 2007, 2010; Henderson et al. 1996, 2001; Himmelstein et al. 1997; Kirman et al. 2010a; Krause and Elfarra 1997; Schmidt and Loeser 1985; Thornton-Manning et al. 1995b). In vitro and perfusion data show that mice are more efficient than rats at oxidizing 1,3-butadiene to form EB, and the conversion of EB to DEB in mice is 3.3-fold greater than in rats and 2.4–61-fold greater than in humans (Kirman et al. 2010a). In addition, mice have a higher ratio of 1,3-butadiene activation to detoxification than rats or humans; the ratio of activation to detoxification was 74:1 in mouse, 6:1 in rat, and 6:1 in human liver tissues (Bond et al. 1993).

Based on my reading of this document, as well as that of Kirman et al., 2022 (especially the data/information provided in section 2), it's my opinion that if a rodent species is to be used to derive any toxicity factor (i.e. RfC) then the most logical choice would be the rat. While differences in the (bio)metabolism of BD still exists between rats and humans, the rat is "more like" that of humans (vs mice). However, it seems to me that the methodology used by Kirman et al., 2022 in that there is now a scientifically-sound ability to account for the large species differences in BD (rat vs human, for example), that can be used to "lower" the uncertainty in the assessment of human health risk to BD.

Expert 2 Explanation

Selected Answer(s): Reference concentration should be based on mouse data

Noncancer toxicity endpoints of concern are ovarian atrophy and fetal body weight changesin rodents mice and rats) specifically in mice. Rats did not claerly demonstrated either endpoint following BD exposure(NTP, 1993; Hackett et al: 1987). Therefore, the the noncancer reference concentration (RfC) should be derived on mouse data.

Expert 1 Explanation

Selected Answer(s): I cannot answer

I am not a toxicologist, never done experiments like these in rodents

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Comments (3)

SCORE 1 **Expert 2** *05/21/2024 09:18*

I think think the mouse database is more appropriate to derive reference concentration (RfC) of BD exposure and fetal body weight changes.The mouse dataset shows fetal body weight changes at all tested dose levels. This effect was not clarly evident in rats and dose-response is also not apparent.I prefer not combining the rodent data.

SCORE **Expert 7** *05/29/2024 08:14*

0 I see the earlier points regarding the use of mouse data to derive the RfC and agree that because of the dose-response observed, these data should be used.

SCORE **Expert 4** *05/29/2024 10:23*

0 Having read all the comments and debate, I still prefer hte use of the combined data sets as described in KIrman et al (2022)

Result 5.3 *(ID: 6366)*
Question 5.3 *(ID: 5737)*

If you selected answer option “e” to the previous question, please indicate if you have any suggested modifications to the methods or data used in Kirman et al. 2022 for implementing the methods of Motwani and Tornqvist (2014) to adjust for species differences for fetal body weight changes.

Expert 5

> I have no modifications to the methods or data to offer at this time.

Expert 7

> I don't have any suggestions - not my area of expertise. Will leave this question to those that do have the expertise....

Expert 2

> None.

Expert 1

> n/a

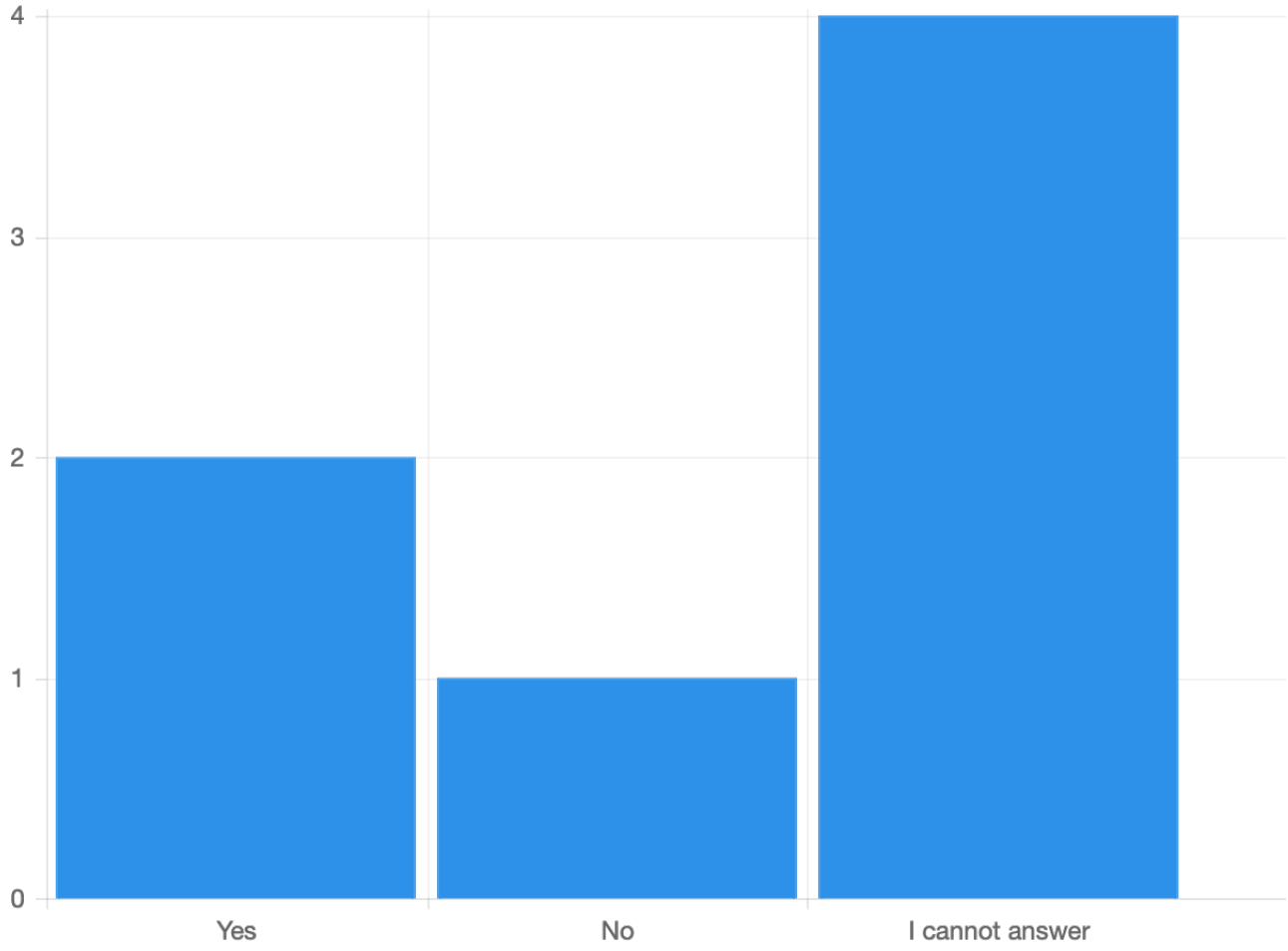
Comments (2)

SCORE **Expert 2** *05/21/2024 09:34*
0 **None.**

SCORE **Expert 7** *05/29/2024 08:14*
0 Nothing to add.

Result 5.4 *(ID: 6367)*
Question 5.4 *(ID: 5738)*

Kirman et al. 2022 relied upon a lower benchmark response rate for the combined rodent continuous data set (decrease of 0.5 standard deviations vs 1 standard deviation) due to the expansion range of observation in the low concentration region with the inclusion of the rat data. Please indicate if you agree with this approach.



Legend

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation
Selected Answer(s): Yes

I agree with the rationale presented in Kirman et al (2022): "Because the combined data set describes a broader range of observation, with rat data characterizing the lowdose region, a response rate of 0.5 standard deviations was considered appropriate for the range of observation defined by the combined data".

Note that the authors also calculated PODs for alternative response rates, which should be included for comparison in a revised document.

Expert 5 Explanation
Selected Answer(s): No

Kirman et al., 2022 chose a BMDL0.5SD value of 860 ppm as the primary basis for the subchronic RfV for BD, saying that "it reflects the data collected in two mammalian species and therefore increases confidence in its extrapolation and application to human health risk assessment." However, the EPA's Benchmark Dose Technical Guidance (2012) clearly states that 1 standard deviation from the control mean should be used unless there is a biologically significant basis for choosing an alternative value. In my opinion, Kirman et al., 2022 fails to provide such a biologically significant basis for the choice of a 0.5 standard deviation. Further, using these data does not increase confidence in extrapolation to the point of departure (POD) because the rat data show no dose-response trend (Table 3 of Kirman et al., 2022 reports the percent fetal body weight change values be 100 ± 6.1 at 0 ppm, 98.6 ± 7.0 at 40 ppm, 97.4 ± 7.3 at 200 ppm and 100.3 ±8 at 1000 ppm). Because of this, when combined with the mouse data, the rat data fail to aid in characterizing dose-response for fetal body weight changes from BD exposures and, in fact, may distort the dose-response modeling results using only the mouse data. As I stated in my response to question 5.1, I am not in favor of combining the rat data with the mouse data for this endpoint because of the lack of dose-response trend and, also, because the rat data only provide a free-standing No-Observed-Adverse-Effect Level.

Expert 7 Explanation
Selected Answer(s): I cannot answer

Lowering the BMR for the BMD modeling of the combined (rats and mice) seems to me to be a conservative approach but beyond saying that, I am not able to make a scientific/statistical argument one way or another.

Expert 1 Explanation
Selected Answer(s): I cannot answer

see above

Comments (2)

SCORE 0 **Expert 2** *05/22/2024 08:33*

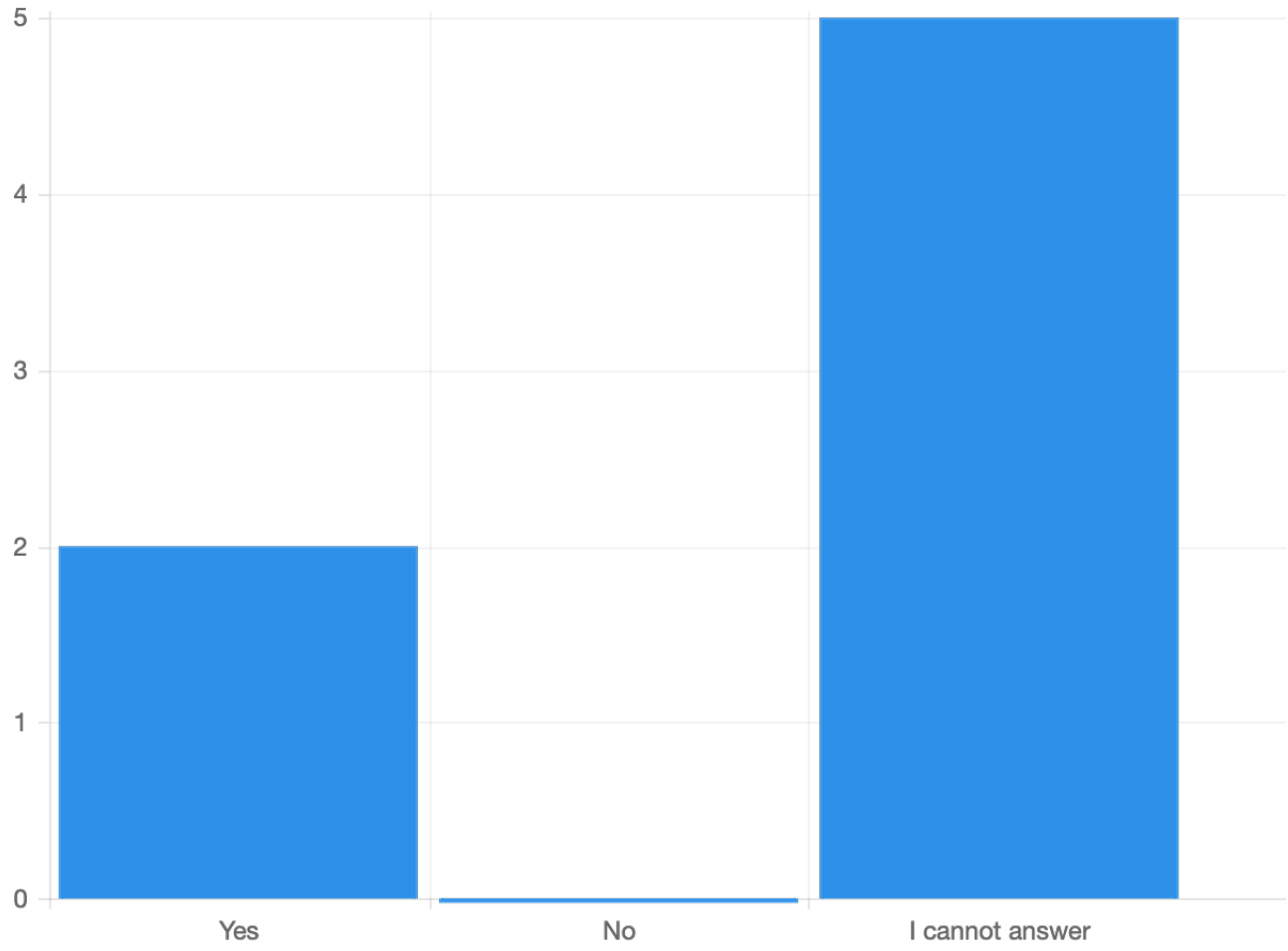
I agree with the comments of Expert 5.I am not in favor of combining the rat data with the mouse data for this endpoint because of the lack of dose-response trend and, also, because the rat data only provide a free-standing No-Observed-Adverse-Effect Level.

SCORE 0 **Expert 7** *05/29/2024 08:18*

It seems that from the previous charge question that the mouse data are favored vs combined mouse and rat. Therefore, as far as comments seen to-date, I agree with Expert 5.

Result 5.5 *(ID: 6369)*
Question 5.6 *(ID: 5740)*

Should the variation in human hemoglobin adducts reported by Boysen et al. (2022; see Table 2) be used to replace the default uncertainty factor for human variation (UFh) for calculating a reference concentration based on fetal body weight effects?



Legend

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation
Selected Answer(s): I cannot answer

I read Boysen et al (2022), but I am unfamiliar with the Collaborative Cross mouse model from which some of the data were taken.

Note that in round 5 I reconsidered the use of the human hemoglobin adduct data. I now think these are useful to consider in the risk assessment.

Expert 5 Explanation
Selected Answer(s): Yes

The data shown in Table 2 of Boysen et al., 2022 should be considered for determining the kinetic portion of the uncertainty factor for human variation (UFh) from BD exposures based on the variation in human hemoglobin adducts. The data on BD occupational exposures and on hemoglobin adducts from human blood samples were analyzed using a linear regression that quantified the relationship between exposure to BD (i.e., the concentrations measured in humans) and the level of hemoglobin adducts in humans. The use of these study results for calculating a reference concentration based on fetal body weight effects is consistent with the EPA's application of data-derived extrapolation factors (USEPA, 2014).

Expert 7 Explanation
Selected Answer(s): I cannot answer

I reviewed the Boysen et al paper (and Kirman and Hayes, 2022) and see the utility of using Hb adducts to derive an intraspecies (human) UF (i.e. potential differences in generation of reactive BD species internally) but am not sure how it would used to arrive at a "non-default" intraspecies sub-UF.

Expert 2 Explanation
Selected Answer(s): I cannot answer

The Boyson et al (2022) study used the avialable published 1,3-butadiene hemoglobin adducts data, as well as the established biomarkers of the internal dose of the reactive epoxides, from several large-scale human studies and from a study in a Collaborative Cross mouse population. They found that in humans, toxicokinetic uncertainty factor for 99th percentile of the population ranged from 3.27 to 7.9, depending on the hemoglobin adduct. In mice, these values ranged from less than 2 to 7.51, depending on the dose and the adducts. I agree with the authors conclusions that quuantitative estimates from this study can be used to reduce uncertainties in the parameter estimates used in the models to derive the inhalation unit risk, as well as to address possible differences in species differences and genetic polymorphisms in enzymes involved in 1,3-Butadiene metabolism that may be dose-related..

Comments (2)

SCORE **Expert 7** *05/29/2024 08:24*
0
Again, I am really not sure how the use of the Hb adduct data would reduce the Intraspecies (human to human) Uncertainty factor. If the risk assessment can make a detailed, scientific argument that this would be useful - then by all means it should be done - just be ready for questions about its use. Otherwise, the use of the "standard" default for intrahuman variation (in OEL, PDE, etc. derivation) = 10 should be strongly considered.

SCORE **Expert 2** *05/29/2024 14:09*
0
I think the he Boyson et al (2022) study used the avialable published 1,3-butadiene hemoglobin adducts data, as well as the established biomarkers of the internal dose of the reactive epoxides, from several large-scale human studies and from a study in a Collaborative Cross mouse population is the most appropriate to replce default uncertainty factor for human variation for derivation of RfC based on fetal body weight changes in rodents.

Result 5.6 *(ID: 6368)*
Question 5.5 *(ID: 5739)*

Kirman et al. 2022 proposed a net uncertainty factor of 30, with a plausible range of 10-100 for an RfC based on fetal body weights. What uncertainty factor values would you recommend for this endpoint?

Uncertainty Factor	1	3	10	Other (please explain)	Total
Interspecies variation (UFa)	0.00% 0	83.33% 5	0.00% 0	16.67% 1	6
Intraspecies variation (UFh)	0.00% 0	33.33% 2	50.00% 3	16.67% 1	6
Subchronic-to-chronic extrapolation (UFs)	66.67% 4	16.67% 1	0.00% 0	16.67% 1	6
LOAEL-to-NOAEL extrapolation (UFl)	83.33% 5	0.00% 0	0.00% 0	16.67% 1	6
Databased uncertaint (UFd)	33.33% 2	50.00% 3	0.00% 0	16.67% 1	6
Other (please explain)	50.00% 3	0.00% 0	0.00% 0	50.00% 3	6

Answer Explanations

Expert 4 Explanation
Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0
Intraspecies variation (UFh)	0	0	1	0
Subchronic-to-chronic extrapolation (UFs)	1	0	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	1	0	0	0
Other (please explain)	1	0	0	0

I generally agree with the UF rationales in Kirman et al (2022). The approaches accounting for interspecies variability were based on appropriaate cross-species toxicokinetic data, obviating the need for a default UFAtk. As there is some indication of variation across species in response to equivalent exposures, a default UFAtd is reasonable.

For UFH, a default factor of 10 appears to encompass both toxicokinetic and toxicodynamic variability.

I feel that no UFD is needed.

Expert 6 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0
Intraspecies variation (UFh)	0	1	0	0
Subchronic-to-chronic extrapolation (UFs)	1	0	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	0	1	0	0
Other (please explain)	1	0	0	0

When studying a certain biomarker in animals the CV measurement within a group are usually 20% therefore, for intraspecies UF of 3 may sufficient.

Expert 5 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0
Intraspecies variation (UFh)	0	0	1	0
Subchronic-to-chronic extrapolation (UFs)	1	0	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	0	1	0	0
Other (please explain)				

The use of a human equivalent concentration (HEC) in exposure-response modeling of the mouse data for fetal body weight accounts for the kinetic portion of uncertainty when extrapolating from mouse to human, essentially setting it equal to 1, leaving a factor of 3 to account for the dynamic portion of UFa. Based on the toxicity data presented to this panel, there is insufficient human data on reproductive and developmental effects from exposures to BD to change the UFh from the default value of 10. The toxicity value for fetal body weight is a Subchronic RfC in Kirman et al. 2022, so the value of UFs should be 1. A LOAEL to NOAEL extrapolation is not being used in this case, so the UFl should be 1. For the database uncertainty factor (UFd), the ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022) states that, “EPA typically follows the suggestion that a factor of 10 be applied if a prenatal toxicity study and a two-generation reproduction study are both missing, and a factor of 10^0.5 (rounded to 3) if either one or the other is missing.” No two-generation studies were provided to the panel, and none is seen in the EPA (2002) document on the Health Assessment of 1,3-Butadiene (see Table 5-1). Hackett et al. (1987) tested CD-1 mice for maternal toxicity, reproductive performance and developmental toxicology, evaluating the female dams and the f1 generation, but did not continue the study to test and evaluate an f2 generation. Thus, based on the studies provided to the panel, the database UFd should be at least a factor of 3. Thus, these UF values result in a composite UF of 100, comprised of a UF of 3 to cover TD differences between species, a default value of 10 for intraspecies variability, and a database UF equal to 3.

Expert 7 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0

Intraspecies variation (UFh)	0	0	1	0
Subchronic-to-chronic extrapolation (UFs)	1	0	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	1	0	0	0
Other (please explain)	1	0	0	0

I read Kirman et al., (2022) discussion of the use of uncertainty sub-factors for the RfC for body weight. I agree with their choices of sub-UFs: Interspecies: a default = 3 is a conservative, health-protective value (though, because the experimental study was via inhalation and human exposure is via inhalation, animals and humans will breathe the same amount of BD based on basal metabolic rate; so could = 1. ; Intraspecies: a default value = 10 is most often used for this sub-factor to be health-protective, especially if the exposed human population can range from young to old, medically compromised to "healthy", etc.; Subchronic to Chronic: exposure during the full period of gestation was done for both rodent species so = 1; LOAEL to NOAEL: either NOAEL of BMDL were used so = 1; Database Uncertainty: for fetal BW there were no apparent data gaps so = 1. Composite UF = 30 is therefore, in my opinion, reasonable.

Expert 2 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0
Intraspecies variation (UFh)	0	1	0	0
Subchronic-to-chronic extrapolation (UFs)	0	1	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	0	1	0	0
Other (please explain)	0	0	0	1

Interspecies UFs for Fetal Body Weight Changes : If one only assumes that mice and humans are equally sensitive to the three primary epoxy metabolites of BD via alkylation of cellular protein macromolecules resulting in cytoxicity and in BW changes, then UF of 1 may be be justified. However, a UF of 3 to account for interspecies variation may be appropriate given sustantial differences in the metabolism of BD in humans and rodents to epoxy metabolites , although qualitatively similar but may be quanitatively different. The fetal body weight changes generally occur due to several risk factors (eg; effect on food intake on exposure to a chemical) during pregnancy in different experimental animal species. as well as in humans . In absence of human epi. data and/ or case reports specific to BD exposure during pregnancy and observations of decrease in fetal weights. it is diificult to argue for application of UF of 1. The net uncertainty factor of 100 may be more reasonable for an RfC based on fetal body weight changes in rodents.

Expert 1 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	0	0	1
Intraspecies variation (UFh)	0	0	0	1
Subchronic-to-chronic extrapolation (UFs)	0	0	0	1
LOAEL-to-NOAEL extrapolation (UFl)	0	0	0	1
Databased uncertaint (UFd)	0	0	0	1

Other (please explain)	0	0	0	1

cannot answer

Expert 3 Explanation
Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)				
Intraspecies variation (UFh)				
Subchronic-to-chronic extrapolation (UFs)				
LOAEL-to-NOAEL extrapolation (UFl)				
Databased uncertaint (UFd)				
Other (please explain)	0	0	0	1

I have no experience in the calculation of uncertainty factors, and therefore default to my colleagues on the panel.

Comments (6)

SCORE **0** **Expert 2** *05/21/2024 11:19*

A review of the Results and comments of Expert opinions seems to agree with the Kirman et al (2022) application of a net uncertainty factor of 30, with a possible range of 10-100 for derivation of RfC based on fetal body weight changes in rodents on BD exposure. Please note that there is insufficient human data on reproductive and developmental effects from exposures to BD to change the UFh from the default value of 10. An intraspecies default value of 10 is often invoked as health protective in absence of the human data and would be difficult to argue with.. An overall database uncertainty factor (UFd) of 1 is also difficult to justify if not well articulated arguments are made based on toxicodynamis (modes / mechanisms of specific target organ toxicity (fetal weight changes) in rodents and potentially in humans on exposure to 1,3- BD during pregnancy. Therefore, I believe a net UFs could be in the range 100 to 300 rather than 10-100 as proposed by Kirman et al (2022).

SCORE **0** **Expert 4** *05/21/2024 14:15*

I would like to offer a point for consideration among the experts. The US EPA Cancer Guidelines (US EPA 2005) moved away from the old paradigm (default unless you can justify departing from it) to a new paradigm: make use of all available relevant data and invoke defaults only when you have to do so. I have seen a lot of retreating from the new paradigm. I would like to see more waving of the "data before defaults" banner.

SCORE **0** **Expert 5** *05/28/2024 12:48*

For the database uncertainty factor (UFd), the ORD Staff Handbook for Developing

IRIS Assessments (EPA, 2022) states that, “EPA typically follows the suggestion that a factor of 10 be applied if a prenatal toxicity study and a two-generation reproduction study are both missing, and a factor of 10^0.5 (rounded to 3) if either one or the other is missing.” Hackett et al. (1987) tested CD-1 mice for maternal toxicity, reproductive performance and developmental toxicology, evaluating the female dams and the f1 generation, but did not continue the study to test and evaluate an f2 generation. Thus, based on the studies provided to the panel, the database UFd should be at least a factor of 3.

SCORE
1

Expert 7

05/29/2024 08:27

I agree that the Composite UF = 30 is very reasonable. People can (and have in my experience) argue and nit-pick about what numerical value should go with what "sub-factor" but this part of toxicity value derivation is, in my opinion, a combination of art/science and experience. The bottom line in most cases seems that the final Composite UF generally comes out to be the same no matter what values goes with what sub-factor....

SCORE
0

Expert 5

05/29/2024 12:29

Given this discussion and further research on uncertainty factors, I am updating my opinion as follows. The use of a human equivalent concentration (HEC) in exposure-response modeling of the mouse data for fetal body weight accounts for the kinetic portion of uncertainty when extrapolating from mouse to human, essentially setting it equal to 1, leaving a factor of 3 to account for the dynamic portion of UFa. Based on the toxicity data presented to this panel, there is insufficient human data on reproductive and developmental effects from exposures to BD to change the UFh from the default value of 10. The toxicity value for fetal body weight is a Subchronic RfC in Kirman et al. 2022, so the value of UFs in that paper is 1, however, if EPA is deriving a chronic RfC using fetal body weight data then UFs should be set equal to 10. A LOAEL to NOAEL extrapolation is not being used in this case, so the UFl should be 1. For the database uncertainty factor (UFd), the ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022) states that, “EPA typically follows the suggestion that a factor of 10 be applied if a prenatal toxicity study and a two-generation reproduction study are both missing, and a factor of 10^0.5 (rounded to 3) if either one or the other is missing.” Hackett et al. (1987) tested CD-1 mice for maternal toxicity, reproductive performance and developmental toxicology, evaluating the female dams and the f1 generation, but did not continue the study to test and evaluate an f2 generation. Thus, based on the studies provided to the panel, the database UFd should be at least a factor of 3. My updated recommendation of the total uncertainty factor for fetal body weight effects is to set it equal to 100 (Ufa=3, UFh=10, UFd=3) if a subchronic RfC is being derived and set it equal to 1000 (Ufa=3, UFh=10, UFs=10, UFd=3) if a chronic RfC is being derived.

SCORE
0

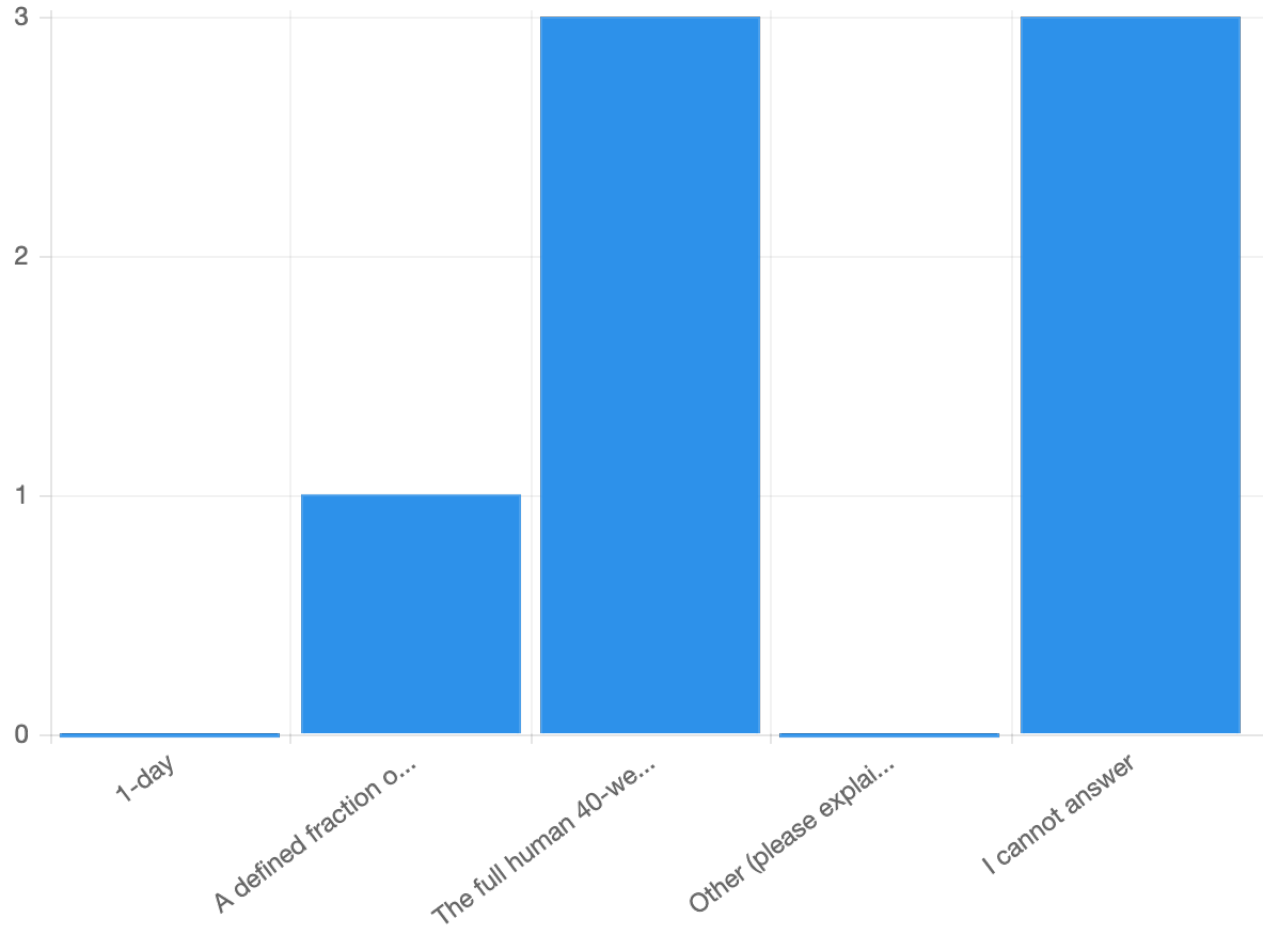
Expert 2

05/29/2024 14:18

Based on a review of the Results and comments of Expert opinions seems to agree with the Kirman et al (2022) application of a net uncertainty factor of 30, with a possible range of 10-100 for derivation of RfC based on fetal body weight changes in rodents on BD exposure. Please note that there is no 2-generation reproductive toxicity and /or human data on reproductive and developmental effects from exposures to BD to change the UFd from the default value of 10.Therefore, I believe a net UFs could be in the range 100 to 300 rather than 30 as proposed by Kirman et al (2022).

Result 5.7 *(ID: 6370)*
Question 5.7 *(ID: 5742)*

The study of Hackett et al. (1987) included exposures to rodents for a substantial fraction of rodent gestation (GD6-15 of a 21-day gestation period). For methods based on best available science, to what exposure duration in humans should these data be compared in order to maintain exposure duration concordance across the exposure assessment and toxicity assessment components of the risk assessment.



Legend

1-day: 0
A defined fraction of the human 40-week gestation period (please specify): 1
The full human 40-week gestation period: 3
Other (please explain): 0
I cannot answer: 3

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation

Selected Answer(s): A defined fraction of the human 40-week gestation period (please specify)

It seems reasonable to use a defined fraction of the human gestation period -- around 48%. However, I defer to the developmental toxicologists in the group, partcularly if the exposure time (not just duration) could have a substantial effect on fetal weight decrease.

Expert 5 Explanation

Selected Answer(s): The full human 40-week gestation period

TSCA should extrapolate the experimental results from Hackett et al. (1987), who exposed female mice to BD for a gestational period of 6-15 days of a 21 day gestation period, to the full human 40-week gestation period in humans.

Expert 7 Explanation

Selected Answer(s): The full human 40-week gestation period

In my experience of deriving health-based OELs and various "toxicity factors", if the critical study selected for the PoD is from a well-conducted developmental toxicity study (i.e. OECD 414, for example) where the entire period of the exposure was for species gestation period, and that PoD (NOAEL, LOAEL, BMDL) is used that the POD would equate (be applicable to) to the full 40-week human gestation period.

Expert 2 Explanation

Selected Answer(s): The full human 40-week gestation period

The developmental toxicity (teratalogy) testing studies in rodents (rats and mice) by regulatory agencies like the US EPA and others have a standard accepted protocol of exposing rodents to a test substance covering a gestational period of 6-15 days of a 21 day geatation period and use this experimental results/data to extrapolate to the full human 40 -week gestation period in humans for chemcal exposure and developmental toxicity risk evaluations. The study of Hackett et al (1987) is appropriate to perform developmental toxicity risk evaliation in absence of any human data.

Comments (2)

SCORE 0 **Expert 2** *05/22/2024 08:40*

The **gestational period of 6-15 days of a 21 day geatation period and use this experimental results/data to extrapolate to the full human 40 -week gestation period in humans for chemcal exposure and developmental toxicity risk evaluations is comparabe. The study of Hackett et al (1987) is very conducted and appropriate to perform developmental toxicity risk evaliation in absence of any human data.**

SCORE 0 **Expert 7** *05/29/2024 08:31*

In my opinion, if the experimental study data results come from the full length of the gestation period for the species (ie say, by using established testing methodology from OECD or EPA) , then this would be more than adequate for direct extrapolation to the human condition of 40-weeks.

Result 5.8 *(ID: 6371)*
Question 5.8 *(ID: 5743)*

If you did not answer "1-day" to the previous question, how should acute human exposures to BD be assessed?

Horizontal bar charts are not supported in the report view.

Answer Explanations

Expert 4 Explanation
Selected Answer(s): Other (please explain)

I feel that the use of the the unadjusted RfC would be a reasonable conservative approach. But I would also expect that the AEGL-1 value should be considered.

Expert 5 Explanation
Selected Answer(s):
Rely on an unadjusted reference concentration derived from Hackett et al. (1987) as a conservative basis

The AEGL-1 for BD is 670 ppm. It is the airborne concentration that represents a threshold level above which it is predicted that the general population, such as infants, children, the elderly, persons with asthma, and those with other illnesses could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. Because BD causes reproductive and development effects in mice and rats, it is unclear whether the AEGL-1 value of 670 ppm would be health protective for pregnant female workers exposed to BD. The Round 3 Summary Report discusses using the Subchronic RfC "as a health-protective surrogate to assess acute exposures to BD. This practice is consistent with the use of fetal body weight effects to derive acute RfVs for BD by other agencies, and it is considered health protective due to differences in exposure duration…" I agree with this conservative approach that would provide protection against developmental effects from single day BD exposures to pregnant women.

Expert 7 Explanation
Selected Answer(s): Other (please explain)

First, I think that the "duration" of acute exposure needs to be defined. I can see "merits" of using either the second or third choice after defining what we want "acute" exposure to define. Is it up to 8-hours as per the EPA AEGL value of 670 ppm (based on focusing in human exposure studies) or should this value be extrapolated, using an additional UF for 24 hour (acute?) exposure (i.e. possibly using 8-hr AEGL-1 x 1/3 = 220 ppm)? Or should the endpoint of developmental toxicity (Hackett et al) be used as was done to obtain either a 6-hour or 24-hour Acute Reference Value (again, what duration of acute are we looking for?).

Expert 2 Explanation
Selected Answer(s): Rely on USEPA's AEGL-1 value based on difficulty focusing in humans

.Acute Exposure Level Guidelines (AEGLs) are used by emergency planners and responders as guidance in dealing with rare, usually accidental, releases of chemicals into the air. AEGLs are expressed as specific concentrations of airborne chemicals such 1,3 - BD at which adverse noncancer health effects may occur. They are designed to protect the adult, elderly and children, and other suceptible individuals (pregnant women) who

may be sensetive to a chemical exposure. They are calculated by the US EPA and OSHA for five relatively short exposure periods – 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours – as differentiated from ambient air standards based on longer or repeated exposures. AEGL “levels” are dictated by the severity of the toxic effects caused by the exposure, with Level 1 being the least and Level 3 being the most severe. I think for the acute exposure to 1, 3 - BD irrespective of noncancer endpoints of chronic toxicity , EPA is likely to follow the AEGL guidelines for differnt durations of exposure (10, 30, minutes, 1, 4, and 8 hrs.).

Comments (2)

SCORE 0

Expert 2

05/22/2024 08:41

I am in full agreement with the comment of Expert 5 on interpretation and derivation of AEGL value for 1, 3- BD. I think OSHA, FEMA and US EPA would use a classical approach using Acute Exposure Guidelines (AEGL) to establish exposure values for different durations (10 min. to 8 hrs) taking into account--extreme health hazard(s) of accidental / plant explosions condtion (s) at a local community level scinarios.

SCORE 0

Expert 7

05/29/2024 08:35

It' my opinion that the use of the EPA AEGL-1 value would be considered as "protective" for short-term exposure to all populations *that is how they, (as well as AIHA ERPG values) are defined/used. I still would like to see "acute" specifically defined in the risk assessment.

Result 5.9 *(ID: 6372)*
Question 5.9 *(ID: 5741)*

Please indicate below any additional issues related to the calculation of a reference concentration for BD based on fetal body weight changes that you would like the panel to consider.

Expert 4

> For all of the health related values, I feel that consideration of likely MOA is paramount. The Kirman et al (2022) paper doesn't explicitly determine a MOA for fetal body weight changes, although I assumed that this was considered among "other effects" as relying on cytotoxicity of butadience metabolites that are alkylating agents.
>
> In a revised document there must be an explicit rationale for choosing fetal body weight changes for only a subchronic RfV. Developmental effects have been used as the critical endpoint for lifetime RfVs.

Expert 7

> None at this time.

Expert 2

> **I would like the Expert Panel to consider the relevance of a RfC for 1,3- BD based on fetal body weight changes in rodents to humans. In humans, genetic and environmental factors are known to influence in utero growth , however, their relative contributions over pregnancy period are unknwn. Environmental factors such as age, nutritional status, adiposity, race, including socio-economc condtions could have an impact during different critical time periods of pregnancy.. Maternal smoking in third trmester of pregnancy is a known to be a strong predictor of birthweight. In humans, maternal undernutrition in early stages of gestation has been linked to number of advese effects on fetal growth and developmet.**

Comments (2)

SCORE **Expert 2** *05/21/2024 11:59*
0 None.

SCORE **Expert 7** *05/29/2024 08:36*
0 None.

Result 6.1 *(ID: 6373)*
Question 6.1 *(ID: 5744)*

As discussed in Kirman et al. (2022), species differences are noted for ovarian atrophy reported in mice and rats exposed to BD, which may be explained by species differences in metabolic activation of BD. Please indicate your preference on the species used to support toxicity values for BD human health risk assessment.

Horizontal bar charts are not supported in the report view.

Answer Explanations

Expert 4 Explanation
Selected Answer(s): Reference concentration should be based on data from both species

Kirman et al (2022) notes that rats exposed directly to DEB are observed with ovarian atrophy. It appears that the species differences for this endpoint are largely a function of the well-described variations in metabolism of butadiene to the active metabolites.

It appears that MOA is the same in both rats and mice.

Thus, I would argue for the use of the larger, relevant data set from both rodent species.

Expert 5 Explanation
Selected Answer(s): Reference concentration should be based on mouse data

Table 2 in Kirman et al. 2022 shows the mouse and rat data for exposures to BD for ovarian atrophy. Ovarian atrophy was observed in mice at all tested concentrations, the lowest of which, 6.25 ppm, was much lower than the concentrations administered to the rats. This effect was not observed in rats at any of the tested concentrations, and no dose-response trend was apparent. For the development of toxicity values, studies in which significant effects are observed are preferred to those not showing effects at any dose level (i.e. the study results in a “free-standing No-Observed-Adverse-Effect-Level” at the highest concentration). Thus, the mouse data would be preferred. A toxicity value for ovarian atrophy does not need to be developed using the rat data, and the datasets should not be combined for the derivation of a Reference Concentration.

Expert 7 Explanation
Selected Answer(s): Reference concentration should be based on rat data

See explanation for Section 5.1.

Expert 2 Explanation
Selected Answer(s): Reference concentration should be based on data from both species

The Kirman et al (2022) very well summarized the ovarian atropy in female mice and rats follwing subchronic and chronic exposure to BD (Table 2). The quantal data sets for the incidence of ovarian atrophy for both species were used separately and combined to support RFC derivation of BD.spanning duration of exposure

from 9 to 105 weeks.The ovarian atrophy as well as fetal body weights in rodents , the same noncancer endpoints were considered previously by the regulatory agencies and are likely to be the relevant choices for any revised noncancer human health risk assessment of BD exposure in absence of any new publihed studies. In vitro and in vivo metabolism studies published so far and physiological model predictions for BD based on levels epoxy metabolites in blood in dfferent species suggest that humans less likely to be as mice regarding formation of BD epoxides and also suggest that humans would be more like rats.Therefore, showing these dffrences in formation of reactive metabolites in based on data in both rodent species and preditionsd in humans to support noncancer toxicity estimation values (RfC) for BD helath risk assessment makes sense and also being transparent .

Comments (2)

SCORE 0

Expert 2

05/21/2024 12:46

My preference is to derive an RfC based on use of rodent data of ovarian atrophy in both the species. Again, the human relevance of these observations in rodents is uncertain and debatable.

SCORE 0

Expert 7

05/29/2024 08:50

I see the Expert's points regarding the use of both rat and mouse ovarian atrophy data in the assessment and agree with their comments.

Result 6.2 *(ID: 6375)*
Question 6.3 *(ID: 5746)*

If you selected answer option “e” to the previous question, please indicate if you have any suggested modifications to the methods or data used in Kirman et al. 2022 for implementing the methods of Motwani and Tornqvist (2014) to adjust for species differences for ovarian atrophy.

Expert 6

> none

Expert 5

> I have no modifications to the methods or data to offer at this time.

Expert 7

> No suggested modification(s).

Comments (2)

SCORE **Expert 2** *05/21/2024 12:20*
0
None at this time.

SCORE **Expert 7** *05/29/2024 08:51*
0
Not able to comment.

Result 6.3 *(ID: 6374)*
Question 6.2 *(ID: 5745)*

Please indicate your preference for adjusting for species differences when extrapolating ovarian atrophy dose-response data from rodents to humans

Horizontal bar charts are not supported in the report view.

Answer Explanations

Expert 4 Explanation
Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

The approach described in Kirman et al (2022) makes the most appropriate use of available data for scaling among species. There is sufficient documentation supporting the utility of hemoglobin adduct measurements in this scaling.

Calculating a human equivalent concentration for each exposure group before running the BMD is preferred to applying an adjustment to the point of departure.

Note that Kirman et al (2022) considered the potential activity of metabolites other than DEB in affecting ovarian atrophy.

Expert 5 Explanation
Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

Based on the information presented to this panel, it seems imperative that differences in metabolic activation be accounted for in the development of toxicity values for BD. Thus, the first three options are not appropriate for use in evaluating BD. In addition, DEB is an important contributor to toxicity, particularly for ovarian atrophy, so the fourth option of internal dose based on PBPK modeling can also be excluded. From Kirman et al. 2022, for the ovarian atrophy effects of BD, the animal to human extrapolation factors for the kinetic portions of uncertainty (EFAKs) are 0.00087 and 0.0162 for mouse to human and rat to human, respectively (calculated from the DEB values in Table 6). These were used to calculate human equivalent concentrations for the mouse and rat data, respectively, accounting for species differences in the internal dose of DEB, to which ovarian atrophy is attributed. This type of EFAK analysis should be used by TSCA to develop human equivalent concentrations for development of Reference Concentrations.

Expert 7 Explanation
Selected Answer(s):

Internal dose based on metabolite-specific hemoglobin adducts (address species differences in metabolic activation for the 3 primary reactive metabolites; per extension of Motwani and Tornqvist, 2014)

See explanation for Section 5.2.

Comments (2)

SCORE 0

Expert 2

05/21/2024 12:38

The approach published as described by the Kirman et al (2022) making use of the most available relevant data in calculation of metabolic specific hemoglobin adducts and addressing species differences in metabolic activation to the most reactive epoxides is the most appropriate to extrapolate ovarian atrophy dose -response from rodents to humans.

SCORE 0

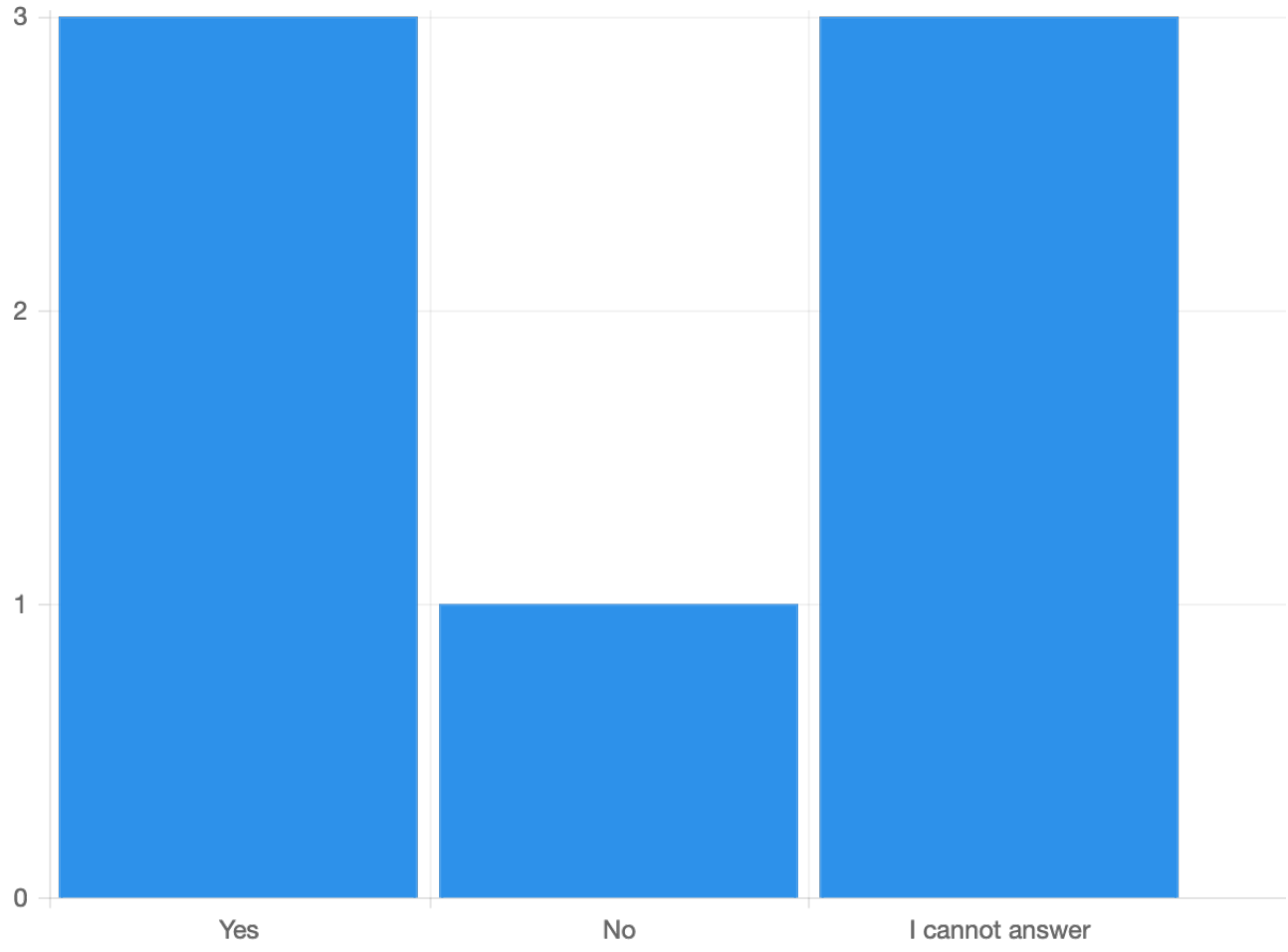
Expert 7

05/29/2024 08:54

Again, I see the validity of the Expert's comments and agree with using the "Internal dose based on metabolite-specific hemoglobin adducts...."

Result 6.4 *(ID: 6376)*
Question 6.4 *(ID: 5747)*

Kirman et al. 2022 relied upon a lower benchmark response rate for the combined rodent dichotomous data set (1% response rate vs 10% response rate) due to the expansion range of observation in the low concentration region with the inclusion of the rat data. Please indicate if you agree with this approach.



Legend

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation
Selected Answer(s): Yes

It is generally preferable to use the lowest BMR that is supported by the data. Thus the choice in Kirman et al (2022) is appropriate and congruent with policies of the US EPA: "Because the combined data set describes a broader range of observation, with the rat data helping to a more complete characterization of the low-dose region, a response rate of 1% was considered appropriate and consistent with selection of a BMR near the low end of the observable range (USEPA, 2012)."

It is useful for provide PODs caculalted with the higher BMRs for comparison.

Expert 5 Explanation
Selected Answer(s): No

Kirman et al. 2022 provide an explanation for the choice of a 1% BMR for ovarian atrophy incidence, citing EPA's Benchmark Dose Technical Guidance (2012) and stating that, "Because the combined data set describes a broader range of observation, with the rat data helping to a more complete characterization of the low-dose region, a response rate of 1% was considered appropriate and consistent with selection of a BMR near the low end of the observable range." However, as I stated in my response to question 6.1, I am not in favor of combining the rat data with the mouse data for this endpoint because of the lack of dose-response trend for ovarian atrophy and because the rat data only provide a free-standing No-Observed-Adverse-Effect Level. (Table 2 of Kirman et al., 2022 reports zero responses out of 110 mice at each of three concentrations, 0, 1000 and 8000 ppm, of BD at 105 weeks.) Using these data does not help characterize the low-dose region because the rat data show no dose-response trend for ovarian atrophy from BD exposures and, in fact, may distort the dose-response modeling results using only the mouse data.

Expert 7 Explanation
Selected Answer(s): Yes

From Table 9 of Kirman et al, 2002, I do see that BMDL01 was used for the combined (mice and rats) and BMDL10 for mouse only [the NOAEL was used as the PoD for rats]. This, as stated, gives increased confidence for use of this PoD for the human health risk assessment because data from two mammalian species are used. I agree that this will give a more conservative, health-based chronic RfC (ie.e. because of the lower starting PoD in the numerator), but I am still not totally convinced that the combined is the "best way to go" since the mouse makes >> more DEB (the putative toxic metabolite for BD ovarian atrophy) that does the rat. But certainly open for discussion on my part....

Expert 2 Explanation
Selected Answer(s): Yes

Yes, I agree with the Kirman et al (2022) approach as described for the combined dichotomous data in rodents. However , we don't know what is the backgound incidence of ovarian atrophy in humans, generally it is likely to be very low. The question of human relevance is daunting and challenging one in absence of epidemiological data on BD exposure and adverse outcome in rodent.

Comments (2)

SCORE 0 **Expert 2** *05/22/2024 08:50*

Yes, I agree with the Kirman et al (2022) approach as described for the combined dichotomous data in rodents. However , we don't know what is the backgound incidence of ovarian atrophy in humans, generally it is likely to be very low. I am not in favor of combining the rat data with the mouse data for this endpoint because of the lack of dose-response trend for ovarian atrophy. The question of human relevance is daunting and challenging one in absence of epidemiological data on BD exposure based alone on observations of adverse outcome of ovarin atrophy in rodents.

SCORE
1

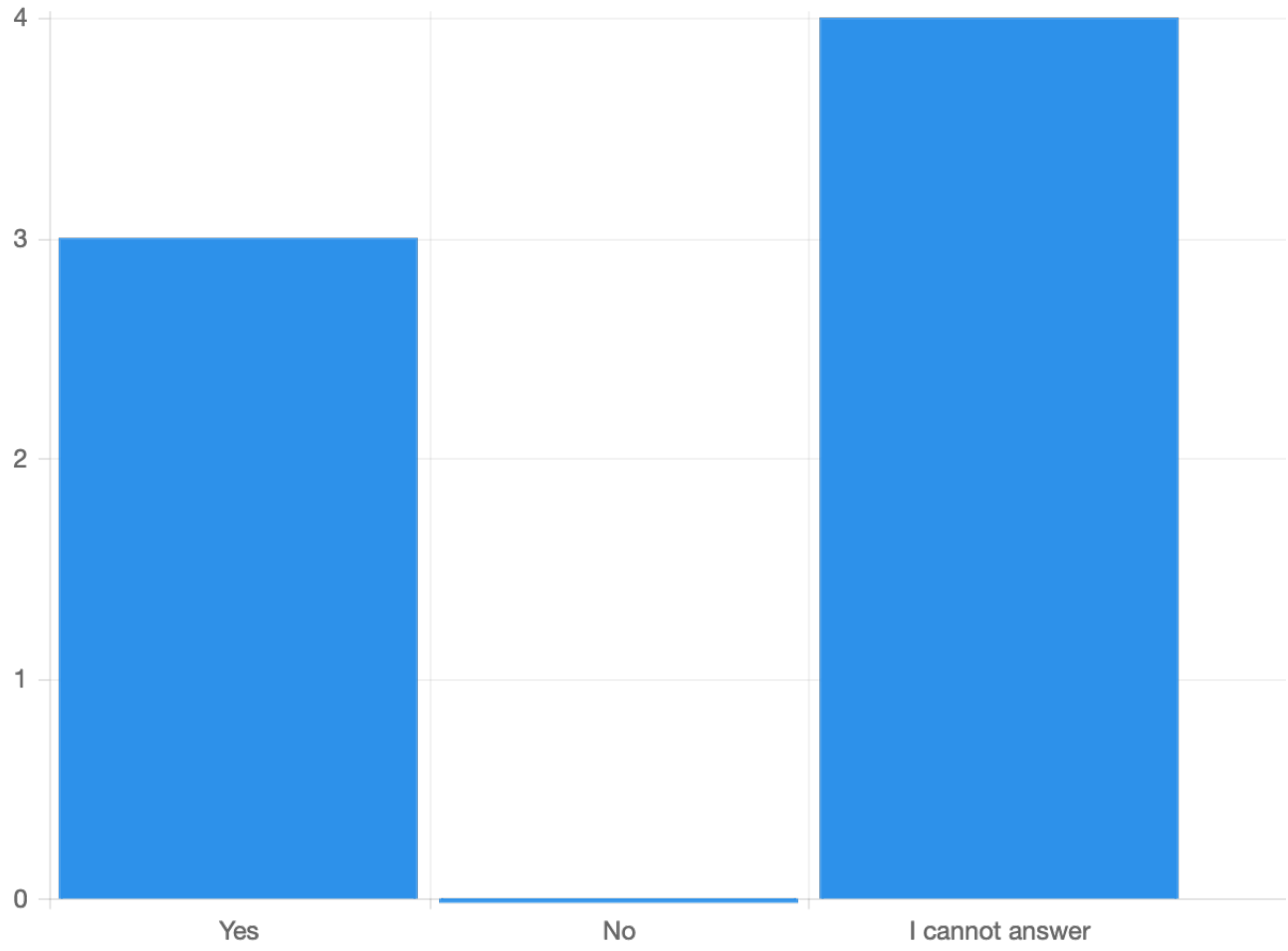
Expert 7

05/29/2024 08:59

In thinking more about it, I think that the use of the BMR 1% (vs 10%) with the expansion of available data in the low concentration region is appropriate. It will, probably? give a more conservative estimate of the PoD, but, seems appropriate because the human exposure concentrations will probably also be in that low concentration region....

Result 6.5 *(ID: 6378)*
Question 6.6 *(ID: 5749)*

Should the variation in human hemoglobin adducts reported by Boysen et al. (2022; see Table 2) be used to replace the default uncertainty factor for human variation (UFh) for calculating a reference concentration based on ovarian atrophy?



Legend

answers: 7
skips: 0

Answer Explanations

Expert 4 Explanation
Selected Answer(s): I cannot answer

I read Boysen et al (2022), but I am unfamiliar with the Collaborative Cross mouse model from which some of the data were taken.

Note that in Round 5 I changed my opinion and now feel that the data on variation in human hemoglobin adducts are useful in calculating the RfC.

Expert 5 Explanation
Selected Answer(s): Yes

The data shown in Table 2 of Boysen et al., 2022 should be considered for determining the kinetic portion of the uncertainty factor for human variation (UFh) from BD exposures based on the variation in human hemoglobin adducts. The data on BD occupational exposures and on hemoglobin adducts from human blood samples were analyzed using a linear regression that quantified the relationship between exposure to BD (i.e., the concentrations measured in humans) and the level of hemoglobin adducts in humans. The use of these study results for calculating a reference concentration based on ovarian atrophy is consistent with the EPA's application of data-derived extrapolation factors (USEPA, 2014).

Expert 7 Explanation
Selected Answer(s): I cannot answer

Again as for 5.6: I reviewed the Boysen et al paper and see the utility of using Hb adducts to derive an intraspecies (human) UF (i.e. potential differences in generation of reactive BD species, etc.) but am not sure how it would used to arrive at a "non-default" intraspecies sub-UF.

Expert 2 Explanation
Selected Answer(s): Yes

I agree with the Boyson et al (2022) use of the availabile published data on 1,3-butadiene hemoglobin adducts, as well as well established biomarkers of the internal dose of the reactive epoxides, from several large-scale human studies and from a study in a Collaborative Cross mouse population to investigate human variation (UFh) for calculating a RfC based on ovarian atrophy. observed in mice. They found that in humans, toxicokinetic uncertainty factor for 99th percentile of the population ranged from 3.27 to 7.9, depending on the hemoglobin adduct while in mice, these values ranged from less than 2 to 7.51, depending on the dose and the hemoglobin adducts. I agree with authors that the quantitative estimates from this study can be used to reduce uncertainties in the parameter estimates used in the models to derive the inhalation unit risk, as well as to address possible differences in variability in 1,3-butadiene metabolism that may be dose-related.

Comments (2)

SCORE **Expert 2** *05/21/2024 13:28*

0

The use of Boyson et al (2022) study results for calculating a reference concentration based on ovarian atrophy is consistent with the EPA's application of data-derived extrapolation factors. I agree with the authors that the quantitative estimates from this study can be used to reduce uncertainties in the parameter estimates used in the models to derive the inhalation unit risk, as well as to address possible differences in human variability in 1,3-butadiene metabolism that may be dose-related. They found that in humans, toxicokinetic uncertainty factor for 99th percentile of the population ranged from 3.27 to 7.9, depending on the hemoglobin adduct while in mice, these values ranged from less than 2 to 7.51, depending on the dose and the hemoglobin adducts. Given the toxicokinetic uncertatinty factors in humans and mice seems to be similar. How this would replace the default uncertainty factor for human variation (UFh) for calculating RfC based on ovarian atrophy in rodents ?

SCORE **Expert 7**

0 I am still not sure how the use of the HB adduct data will affect the human to human (intraspecies) UF. Like I noted in the pervious round for noncancer, if adequate scientific justification is put forward, by all means use it...but if not, use the standard default = 10 *05/29/2024 09:01*

Result 6.6 *(ID: 6377)*
Question 6.5 *(ID: 5748)*

Kirman et al. 2022 proposed a net uncertainty factor of 30, with a plausible range of 10-100 for an RfC based on ovarian atrophy. What uncertainty factor values would you recommend for this endpoint?

Uncertainty Factor	1	3	10	Other (please explain)	Total
Interspecies variation (UFa)	20.00% 1	60.00% 3	0.00% 0	20.00% 1	5
Intraspecies variation (UFh)	0.00% 0	20.00% 1	60.00% 3	20.00% 1	5
Subchronic-to-chronic extrapolation (UFs)	60.00% 3	20.00% 1	0.00% 0	20.00% 1	5
LOAEL-to-NOAEL extrapolation (UFl)	60.00% 3	20.00% 1	0.00% 0	20.00% 1	5
Databased uncertaint (UFd)	20.00% 1	60.00% 3	0.00% 0	20.00% 1	5
Other (please explain)	40.00% 2	0.00% 0	0.00% 0	60.00% 3	5

Answer Explanations

Expert 4 Explanation
Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0
Intraspecies variation (UFh)	0	0	1	0
Subchronic-to-chronic extrapolation (UFs)	1	0	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	1	0	0	0
Other (please explain)	1	0	0	0

Calculation of human equivant concentrations adjusts for UFAtk variability and uncertaninty. A default UFAtd is reasonable.

Kirman et al (2022) note that biomarker studies for butadiene support a UFHtk of 3 as covering the reasonable range of variability. Consideration of variabililty in follicle counts and resulting sensitivity to butadiene in reducing counts lends support to a UFHtd of 3 for a combined UFH of 10.

No UF are needed for LOAEL - NOAEL extrapolation as the PODs are calculated by benchmark dose modelling using relevant data. The study durations for observation of ovarian atrophy are considered close to lifetime, so UFS = 1.

Kirman et al (2022) makes a salient point that the data base for ovarian atrophy is lacking on early key events such as follicle depletion. I would discuss this as an area of uncetainty, but I would not apply a UFD greater than 1.

Expert 5 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0
Intraspecies variation (UFh)	0	0	1	0
Subchronic-to-chronic extrapolation (UFs)	1	0	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	0	1	0	0
Other (please explain)				

The use of a human equivalent concentration (HEC) in exposure-response modeling of the mouse data for ovarian atrophy accounts for the kinetic portion of uncertainty when extrapolating from mouse to human, essentially setting it equal to 1, leaving a factor of 3 to account for the dynamic portion of UFa. Based on the toxicity data presented to this panel, there is insufficient human data on reproductive and developmental effects from exposures to BD to change the UFh from the default value of 10. The toxicity value for ovarian atrophy is based on a chronic study, so the value of UFs should be 1. A LOAEL to NOAEL extrapolation is not being used in this case, so the UFl should be 1. For the database uncertainty factor (UFd), the ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022) states that, “EPA typically follows the suggestion that a factor of 10 be applied if a prenatal toxicity study and a two-generation reproduction study are both missing, and a factor of 10^0.5 (rounded to 3) if either one or the other is missing.” No two-generation studies were provided to the panel, and none is seen in the EPA (2002) document on the Health Assessment of 1,3-Butadiene (see Table 5-1). Hackett et al. (1987) tested CD-1 mice for maternal toxicity, reproductive performance and developmental toxicology, evaluating the female dams and the f1 generation, but did not continue the study to test and evaluate an f2 generation. Thus, based on the studies provided to the panel, the database UFd should be at least a factor of 3. Thus, these UF values result in a composite UF of 100, comprised of a UF of 3 to cover TD differences between species, a default value of 10 for intraspecies variability and a database UF set equal to 3.

Expert 7 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	1	0	0	0
Intraspecies variation (UFh)	0	0	1	0
Subchronic-to-chronic extrapolation (UFs)	1	0	0	0
LOAEL-to-NOAEL extrapolation (UFl)	1	0	0	0
Databased uncertaint (UFd)	0	1	0	0
Other (please explain)	1	0	0	0

I reviewed Kirman et al., 2022 and TCEQ 2014. For Interspecies: I agree with the references consulted + for interspecies if the route of experimental exposure = route of human exposure, the amount breathed in is equivalent because it is based on basal metabolic rate. For Interspecies = 1. For Intraspecies: Default for human

populations based on potential differences in metabolism, age, health, etc. For Subchronic to Chronic: 2-year bioassay used so = 1. LOAEL to NOAEL: BMDL01 used so use as a very conservative NOAEL so = 1. Database Uncertainty: Agree with rational in references so = 3.

Expert 2 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)	0	1	0	0
Intraspecies variation (UFh)	0	1	0	0
Subchronic-to-chronic extrapolation (UFs)	0	1	0	0
LOAEL-to-NOAEL extrapolation (UFl)	0	1	0	0
Databased uncertaint (UFd)	0	1	0	0
Other (please explain)	0	0	0	1

I think the a net uncertainty factor of 30 by Kirman et al is well justified , however , having no published epidemilogical studies and/ or case reports in humans on BD exposure and ovarian atrophy observations and derivation of RfCs are based on chronic exposure as routinly developed by the regulatory agencies , a plausible range of UFs is likely to be 100-300.

Expert 3 Explanation

Selected Answer(s):

Uncertainty Factor	1	3	10	Other (please explain)
Interspecies variation (UFa)				
Intraspecies variation (UFh)				
Subchronic-to-chronic extrapolation (UFs)				
LOAEL-to-NOAEL extrapolation (UFl)				
Databased uncertaint (UFd)				
Other (please explain)	0	0	0	1

As above, I have no experience and default to my colleagues.

Comments (4)

SCORE 0

Expert 5 *05/28/2024 13:20*

For the database uncertainty factor (UFd), the ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022) states that, “EPA typically follows the suggestion that a factor of 10 be applied if a prenatal toxicity study and a two-generation reproduction study are both missing, and a factor of 10^0.5 (rounded to 3) if either one or the other is missing.” Although ovarian atrophy effects were reported in several chronic reproductive studies (NTP, 1984, 1993; Bevan et al., 1996), no two-generation studies were provided to the panel and none is seen in the EPA (2002) document on the Health Assessment of 1,3-Butadiene (see Table 5-1). Hackett et al. (1987) tested CD-1 mice for maternal toxicity, reproductive performance and developmental toxicology, evaluating the female dams and the f1 generation, but did not continue the study to test and evaluate an f2 generation. Thus, based

on the studies provided to the panel, the database UFd should be at least a factor of 3.

SCORE 0 **Expert 7** *05/29/2024 09:02*

As before for noncancer, I agree that the Composite UF = 30 is very reasonable. People can (and have in my experience) argue and nit-pick about what numerical value should go with what "sub-factor" but this part of toxicity value derivation is, in my opinion, a combination of art/science and experience. The bottom line in most cases seems that the final Composite UF generally comes out to be the same no matter what values goes with what sub-factor....

SCORE 0 **Expert 5** *05/29/2024 12:31*

Given this discussion and further research on uncertainty factors, I am updating my opinion as follows. In Kirman et al. 2022, the human equivalent dose (HED) in dose-response modeling of the mouse data for ovarian atrophy accounts for the kinetic portion of animal to human uncertainty, essentially setting it equal to 1, leaving a factor of 3 to account for the dynamic portion of UFa. Based on the toxicity data presented to this panel, there is insufficient human data on reproductive and developmental effects from exposures to BD to change the UFh from the default value of 10. The toxicity value for ovarian atrophy is based on a chronic study, so the value of UFs should be 1. A LOAEL to NOAEL extrapolation is not being used in this case, so the UFl should be 1. For the database uncertainty factor (UFd), the ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022) states that, “EPA typically follows the suggestion that a factor of 10 be applied if a prenatal toxicity study and a two-generation reproduction study are both missing, and a factor of 10^0.5 (rounded to 3) if either one or the other is missing.” Although ovarian atrophy effects were reported in several chronic reproductive studies (NTP, 1984, 1993; Bevan et al., 1996), no two-generation studies were provided to the panel, and none is seen in the EPA (2002) document on the Health Assessment of 1,3-Butadiene (see Table 5-1). Hackett et al. (1987) tested CD-1 mice for maternal toxicity, reproductive performance and developmental toxicology, evaluating the female dams and the f1 generation, but did not continue the study to test and evaluate an f2 generation. Thus, based on the studies provided to the panel, the database UFd should be at least a factor of 3. My updated recommendation of the total uncertainty factor for ovarian atrophy is to set it equal to 100 (Ufa=3, UFh=10, UFd=3).

SCORE 0 **Expert 2** *05/29/2024 14:28*

In my opinion, the a net uncertainty factor of 30 by Kirman et al is justified , however , having no published epidemilogical studies and/ or case reports in humans on BD exposure and

ovarian atrophy observations and derivation of RfCs are based on chronic exposure as routinly developed by the regulatory agencies , a plausible range of UFs is likely to be selected 100-300.

Result 6.7 *(ID: 6379)*
Question 6.7 *(ID: 5750)*

Please indicate below any additional issues related to the calculation of a reference concentration for BD based on ovarian atrophy that you would like the panel to consider.

Expert 4

The summary document provides no rationale for the choice of critical endpoint, beyond noting that authoritative bodies have used this in the past. This is insufficient.

A discussion of the MOA presented in Kirman et al (2022) would add greatly to an understanding of the choices made in the derivation of the chronic reference value.

In general I prefer an almost boringly explicit listing of the decision points (choice of enpoint, choice of data sets, modelling choices, etc.) and the rationale for each. Clarity in this presentation supports objective discussion of the pros and cons (and implications) of each choice.

Expert 7

None at the present.

Expert 2

Human relevance of ovarian atrophy observed in rodents needs to be well articulated comparing species differerces in toxicokinetics and toxicodynamics of 1,3 BD and its reactive metabolites to elicit ovarian toxicity. Based on currently avialable PK data , it seems that humans are likely to produce less epoxides such as DEB than in mice. The PBPK model(s) need to be validated to predict distribution of major metabolites of BD in different species.Variation in ovarian follicle count in mice, rats and humans and sensitivity to the adverse effect (ovarian atrophy) and follicle depletion) should be claerly described and considered in quantitative noncancer risk assessment based on ovarian atrrophy. I would like to note that cigarette smoking and other environmental and genetic factors in women have been found to hasten the onset of menapause due to depletion of oocytes during the reproductive age. The extent to which toxicokinetic and toxicodynamic mechanisms are similar or dissimilar in rodents and humans are likely to dictate the appropratenss of the use of animal toxicity data for their relevance in human health risk assessment of 1,3- BD.

Expert 1

n/a

Comments (3)

SCORE **Expert 4** *05/21/2024 14:27*
0
I agree with Expert 2 re points on the relevance of rodent ovarian atrophy to human health.

SCORE **Expert 2**

0 I suggest to prepare a draft summary report of deliberation of the Expert Panel following the approach and format of the recent publicatiion of the US EPA " ORD Staff Handbook for Developing Risk Assessments (EPA/600/R22/268, 2022)" . This approach is very well accepted within the agency's regulatory programs for hazard and dose-response characterization of environmental agents evaluated for implementation of regulatory statutes . The regulatory programs of US EPA primarily use the IRIS / ORD chemical noncancer and cancer risk assessments for their regulatory rule making.

05/22/2024 08:59

SCORE
0 **Expert 7**

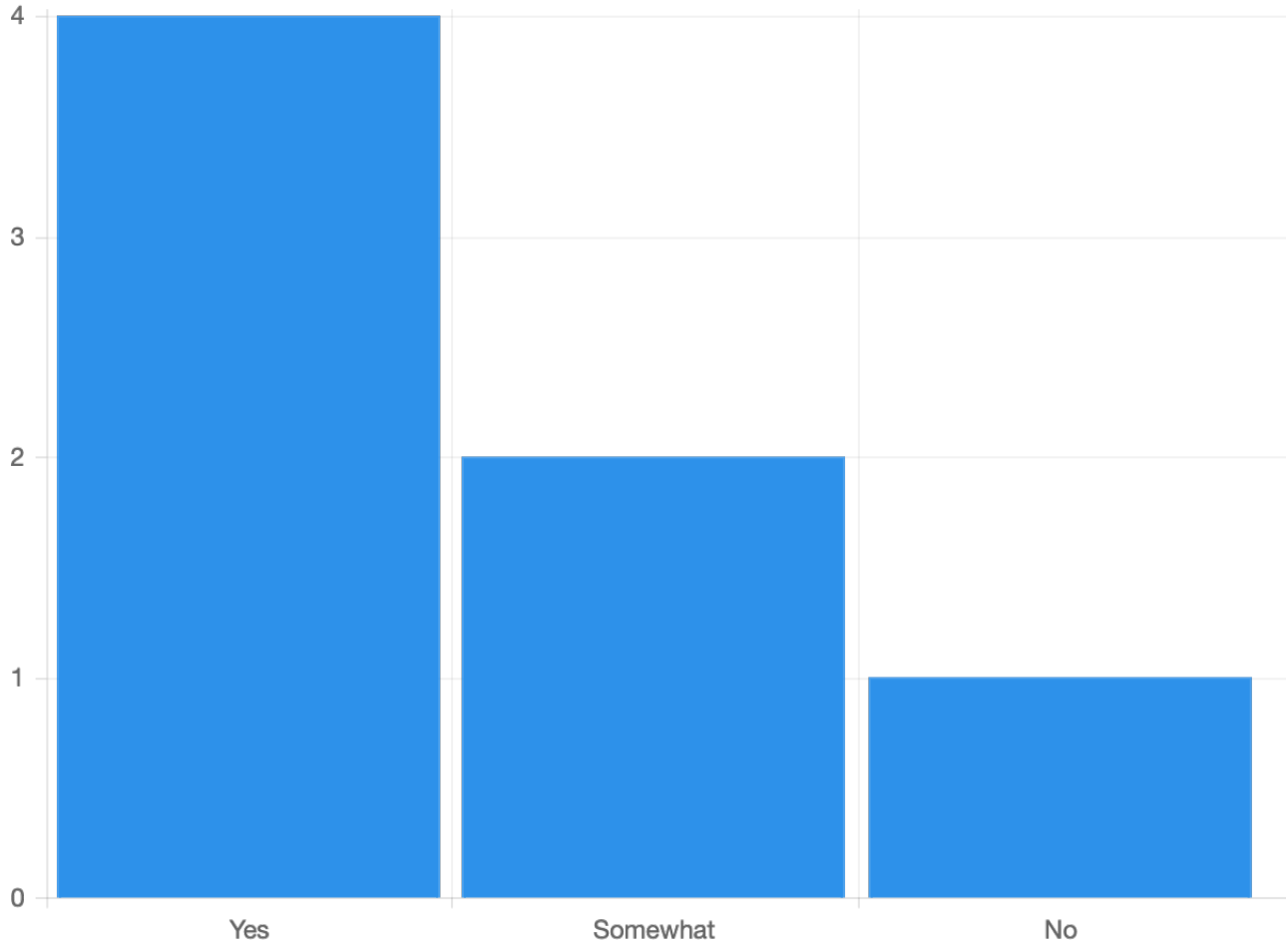
I like Expert 2's comment.

05/29/2024 09:03

ROUND 5 CHARGE QUESTIONS

Result 7.1 *(ID: 6413)*
Question 7.1 *(ID: 5806)*

In Section 2 of the Round 5 Summary Report we make a recommendations to: (1) proceed with the CPH regression-based results of Valdez-Flores et al. (2022); (2) explicitly identify the critical assumption of CPH application for for risk assessment purposes; and (3) include text in the discussion section that describes potential future refinements to modeling and the need for guidance development. Please indicate if you feel this is a reasonable approach.



Legend

answers: 7
skips: 0

Answer Explanations

Expert 7 Explanation
Selected Answer(s): Yes

I agree with points 1-3 (above). As stated in the Summary Material, this is the approach that is used by authoritative bodies such as the US EPA and the TCEQ (who does very good work, in my opinion).

Expert 5 Explanation
Selected Answer(s): Somewhat

The use of the CPH regression model seems to be a reasonable method for analyzing mortality resulting from leukemia and bladder/urinary cancers associated with BD exposed SBR workers. Valdez-Flores et al. (2022) highlight the importance of covariates such as age (already incorporated into the model), sex, cumulative number of BD Hits and cumulative number of styrene HITs (Tables 5 and 6). Because these covariates show a pattern of being statistically significant, they should be considered for inclusion in the final models used by TSCA. Regarding the proportional hazard assumption, I don't see where Valdez-Flores et al. (2022) tried to test this assumption or other model characteristics. The website, Statistical Tools for High-Throughput Data Analysis (http://sthda.com/english/wiki/cox-model-assumptions) provides the following information:

"The Cox proportional hazards model makes several assumptions. Thus, it is important to assess whether a fitted Cox regression model adequately describes the data. Here, we'll discuss three types of diagnostics for the Cox model:

- Testing the proportional hazards assumption.
- Examining influential observations (or outliers).
- Detecting nonlinearity in relationship between the log hazard and the covariates.

In order to check these model assumptions, *Residuals* method are used. The common residuals for the Cox model include:

- *Schoenfeld residuals* to check the proportional hazards assumption
- *Martingale residual* to assess nonlinearity
- *Deviance residual* (symmetric transformation of the Martinguale residuals), to examine influential observations".

(There may be other ways to test the CPH assumptions that I am unaware of.) While I think it is fine to "describe potential future refinements to modeling and the need for guidance development", I see no reason to ignore conducting tests of the CPH assumptions, especially since they may turn out to be confirmed, strengthening the results of the modeling.

Expert 4 Explanation
Selected Answer(s): Yes

The arguments in the Round 5 Summary Report appeared cogent. If the assumption of CPH is described explicitly in a revised report, this rationale would serve as the basis for objective evaluation of its appropriateness. I would support outlining future modelling refinements as well as calling for the development of peer reviewed guidance.

Expert 6 Explanation
Selected Answer(s): Somewhat

Not my expertise - I defer to statisticians in the panel.

Expert 3 Explanation
Selected Answer(s): Yes

I defer to my colleagues for the details, but the write up and recommendation sound reasonable to me.

Expert 2 Explanation
Selected Answer(s): Yes

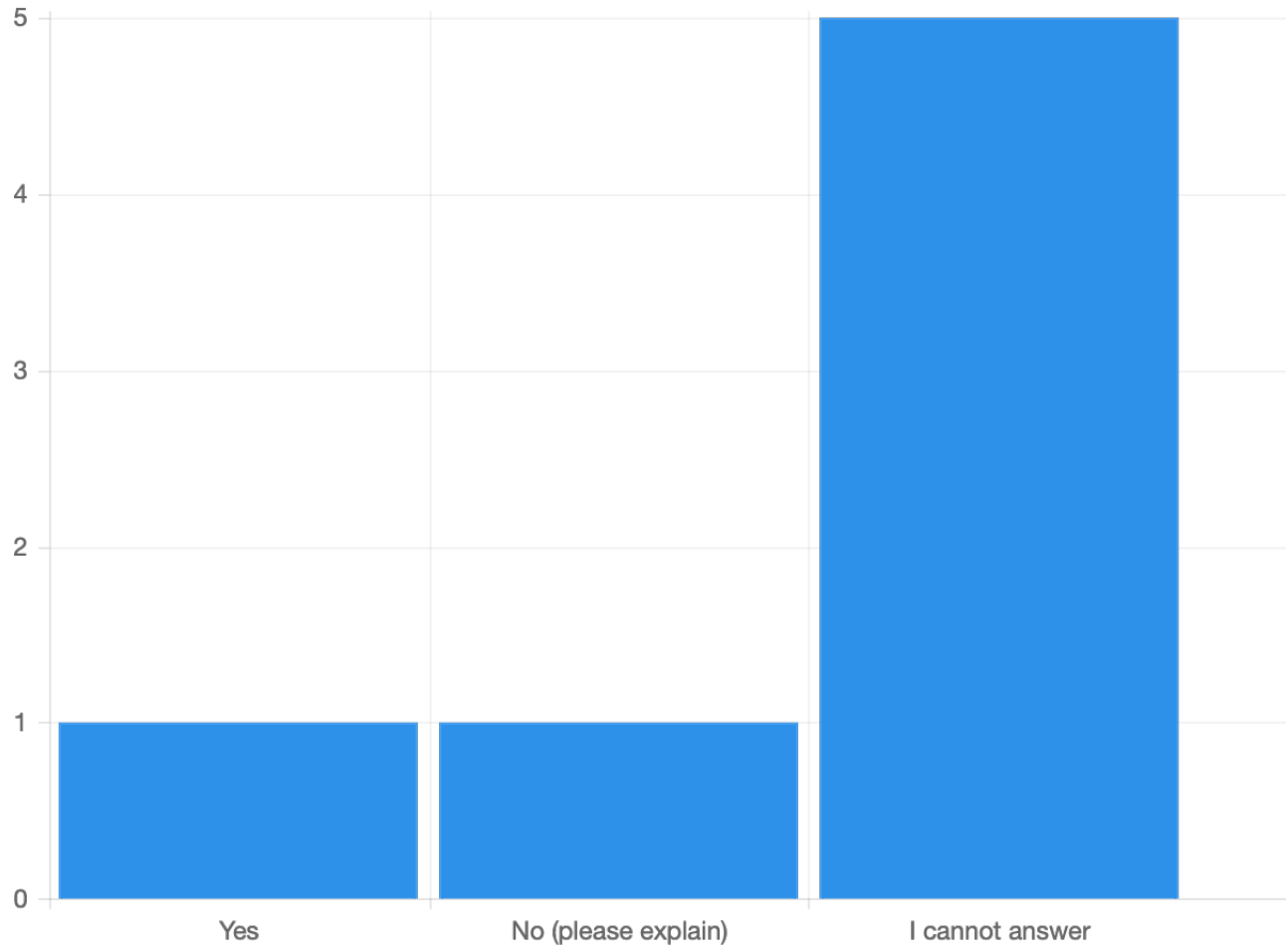
I agree with the three recommendations as proposed.

Expert 1 Explanation
Selected Answer(s): No

The arguments in the report are too superficial to convince me that hazard is constant over time-dependent factor, e.g. age or accumulated exposure, simply because cumulative exposure metric was used and partial iso full likelihood was used (why should the estimation method matter to structural assumptions of the model?). I may be wrong, but I am not convinced by the arguments in front of me. Looking at the cited reference, it states "The Cox proportional hazards model is used here to fit the most recent SBR study data. The Cox model assumes that the baseline hazard rate … is a function of time (age) and that the hazard rate ratio (RR), in addition to cumulative exposures, depends on [baseline hazard rate] and the effect of multiplicative covariates." This is a standard approach, not some exotic variant that makes it unnecessary to test for proportional hazards assumption. The quote from Allison book simply states that if hazards do not vary over time very much, averaging them may be OK -- it is not a permission ignore and never test PH assumption. Do not know what else to say... This is taught in intro to survival analysis, and I am not saying anything controversial.

Result 7.2 *(ID: 6414)*
Question 7.2 *(ID: 5807)*

In Sathiakumar et al. (2021b), the authors relied upon an indirect method to assess the potential confounding by smoking (i.e., relying on COPD mortality)? Do you consider these methods to be appropriate and sufficient?



Legend

answers: 7
skips: 0

Answer Explanations

Expert 7 Explanation
Selected Answer(s): I cannot answer

I will leave the answer to this to the Experts in Epidemiology.

Expert 5 Explanation
Selected Answer(s): No (please explain)

COPD and lung cancer are not the cancer endpoints of concern from BD exposures; thus, I don't find the use of data on these endpoints to be compelling for application to the risk assessment of BD.

Expert 4 Explanation
Selected Answer(s): I cannot answer

I re-read Sathiakumar et al (2021b), but I lack sufficient expertise to critque their method and conclusions

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Expert 3 Explanation
Selected Answer(s): I cannot answer

Beyond my expertise.

Expert 2 Explanation
Selected Answer(s): Yes

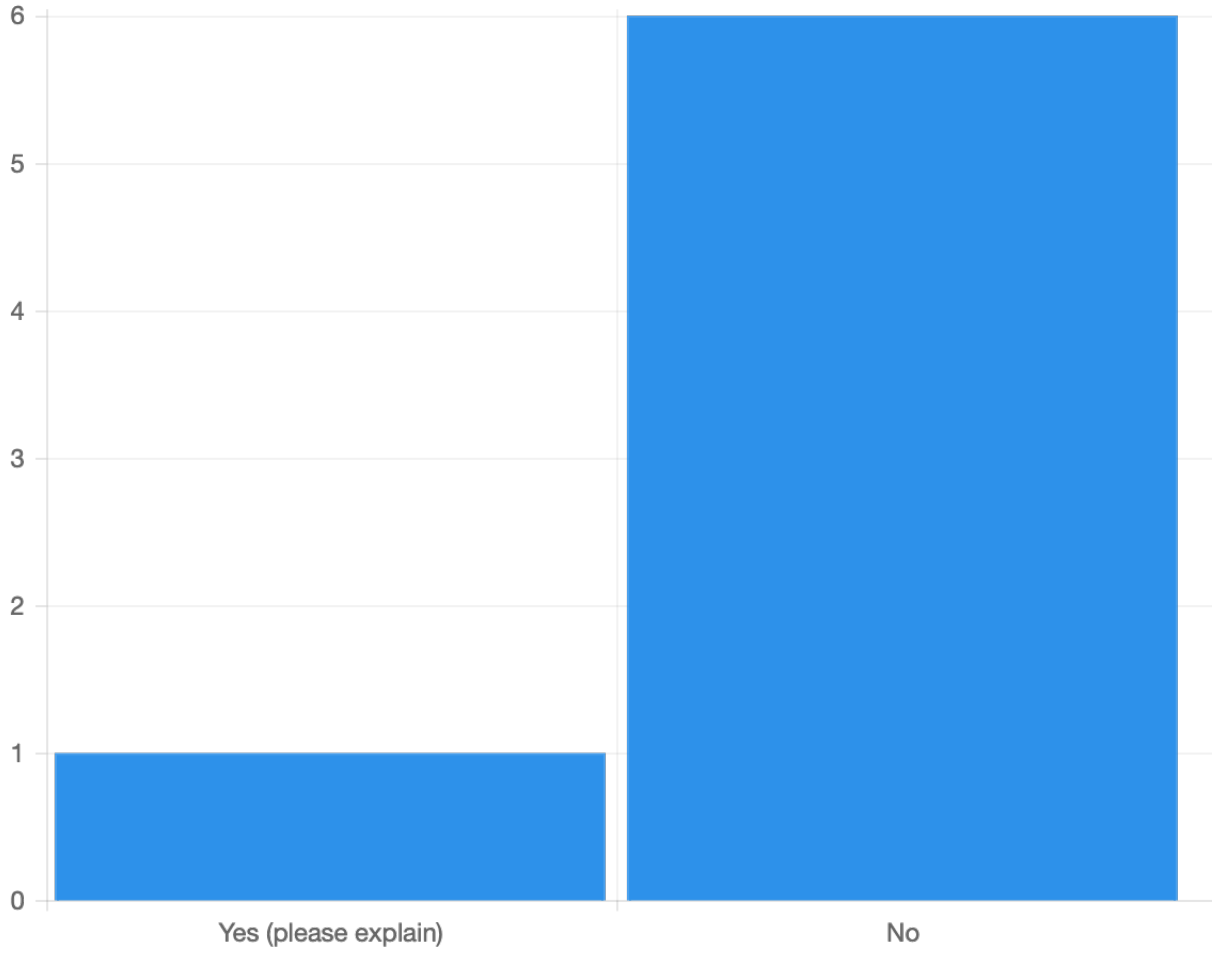
I am fine with the Sethikumar et al (2021b) approach to assess the potential confounding by smoking and its contribution to COPD mortatlity using the indirct method..

Expert 1 Explanation
Selected Answer(s): I cannot answer

This is not addressed in summary report. Lack of association of BD with COPD may indicate that there is no issue with confounding by smoking, especially if holds true for other smoking-related outcomes, and BD does not cause COPD. Lack of association with COPD and NMRD is not apparent in the reference (it is hard to prove the negative): "For butadiene and COPD, the RR was slightly above 1.0, but
not statistically significant, in each quartile of exposure. The exposure response trend was statistically significant and positive in analyses that included all person-time ... but ...". Lack of effect on lung cancer is more reassuring, to be honest, but it is a messy situation. Sensitivity analyses by unmeasured smoking that I suggested are simpler and easier to interpret.

Result 7.3 *(ID: 6415)*
Question 7.3 *(ID: 5808)*

Do you have a suggestions for modifying the equations for occupational exposure value calculation provided in Section 3 of the Round 5 Summary Report?



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answers: 7
skips: 0

Answer Explanations

Expert 7 Explanation
Selected Answer(s): No

I reviewed the Section 3 equations for both non-caner and caner endpoints and based on their use in the recent Formaldehyde assessment, and in in my own experience with what EPA is looking for in an OEV, I agree that these two equations are very reasonable to use.

Expert 5 Explanation
Selected Answer(s): Yes (please explain)

I have very limited experience with exposure modeling, so I hope my comments are useful because I found a few aspects of the equations to be unclear. The units for each of the terms in these equations need to be specified. For

OEVnc, I assume from the equation that they are ppm/yr of BD, unless you meant to divide by (ET x EF x ED) instead of (ET x EF) and then OEVnc would be in ppm, same as PODHEC. MOE should be annotated so that it is clear that it really means the Benchmark MOE, maybe use MOEb to be distinct from MOE, or just use Total Uncertainty Factor instead. For OEVc, I assume from the equation that it is in units of ppm, but the units for TR are not given.

Expert 4 Explanation
Selected Answer(s): No

I am generally OK with the equations in the Round 5 Summary Report, with the exception of some difficulties in what I see as interpretation of MOE. As noted below (7.4) the determination of acceptability of a MOE is a risk management decision, generally determined through risk policy or requirements of an enabling legislation. A MOE is not equivalent to an UF. The acceptability of the former may be informed by a consideration of the latter, particularly by rationales for choices among components of the total UF.

What risk assessors have done is to propose a range of acceptable MOE to use in Eq1, usually as part of problem formulation. This is not just semantics, and I would delete this text from the MOE explanation "(or total uncertainty factor)". While risk mangement choices are based in part on appropiate risk assessments, these are independent processes. I hope this was emphasized in US EPA (2014), Framework for Human Health Risk Assessment to Inform Decision Making, available at https://www.epa.gov/sites/default/files/2014-12/documents/hhra-framework-final-2014.pdf .

Expert 6 Explanation
Selected Answer(s): No

They look fine to me.

Expert 3 Explanation
Selected Answer(s): No

As previously discussed these equations are sufficient for the risk assessment of BD.

Expert 2 Explanation
Selected Answer(s): No

None.

Result 7.4 *(ID: 6416)*
Question 7.4 *(ID: 5809)*

In Round 3, a net uncertainty factor value (and margin of exposure) of 30 was identified as the panel mode for assessing the potential hazards for ovarian atrophy and fetal body weight changes for general population exposures to BD. Because the general population includes subpopulations not included in the work force, how should the uncertainty factor values for calculating occupational exposure levels be modified for the protection of workers?

Expert 7

Based on the following from my experience in deriving health-based Occupational Exposure Limits (OELs), I would suggest going from a "10" to a "3" for the intraspecies sub-UF (while keeping the other UFs the same....):

The intraspecies (interindividual) variation uncertainty factor is intended to account for the variation in sensitivity among humans (for developing OELs, the human population under consideration is the worker population) and is thought to be composed of toxicokinetic and toxicodynamic uncertainties. Default factor for workers = 3 (ECETOC and others) The default value of 3 is recommended for the homogeneous worker population. In this population, the more susceptible (sub)groups are typically excluded and/or may be protected from specific exposures. Thus, the normal hygiene practices that are used/required in the workplace can serve to compensate in the management of risk and lower values of the assessment factor for intraspecies variability are considered appropriate. In addition, based on an overall intraspecies assessment (extrapolation) factor for workers = 3, the individual factors for toxicokinetics = 1.5 and toxicodynamics = 2 would represent the 90th percentile of the combined distribution of toxicokinetic and toxicodynamic variability. Therefore, refinement of the intraspecies default factor of 3 may be possible depending on the amount of data/information available regarding the toxicokinetic and/or toxicodynamic properties of the chemical in the adult worker population.

Expert 5

In Kirman et al. 2022, the human equivalent dose (HED) in dose-response modeling of the mouse data for ovarian atrophy and for fetal body weight effects accounts for the kinetic portion of animal to human uncertainty, essentially setting it equal to 1, leaving a factor of 3 to account for the dynamic portion of UFa. Based on the toxicity data presented to this panel, there is insufficient human data on reproductive and developmental effects from exposures to BD to change the UFh from the default value of 10. Because there are female workers who are in the age range where they could become pregnant, I don't see any need to reduce this value for occupational workers. For both endpoints, the value of UFs should be 1 and the value of UFl should also be 1. For the database uncertainty factor (UFd), the ORD Staff Handbook for Developing IRIS Assessments (EPA, 2022) states that, "EPA typically follows the suggestion that a factor of 10 be applied if a prenatal toxicity study and a two-generation reproduction study are both missing, and a factor of 10^0.5 (rounded to 3) if either one or the other is missing." No two-generation studies were provided to the panel, and none is seen in the EPA (2002) document on the Health Assessment of 1,3-Butadiene (see Table 5-1). Hackett et al. (1987) tested CD-1 mice for maternal toxicity, reproductive performance and developmental toxicology, evaluating the female dams and the f1 generation, but did not continue the study to test and evaluate an f2 generation. Thus, based on the studies provided to the panel, the database UFd should be at least a factor of 3. My updated recommendation of the Total Uncertainty Factor for ovarian atrophy and for

fetal body weight effects for occupational workers is to set it equal to 100 (Ufa=3, UFh=10, UFd=3). However, I agree with using the information in Table 2 of the Round 5 Summary Report to develop a data derived value for the kinetic portion of the uncertainty factor for human variation (UFh) from BD exposures based on the variation in human hemoglobin adducts, so this would impact the final Total Uncertainty Factor used by TSCA.

Expert 4

A margin of exposure is merely the estimated or measured no adverse effect level (or chosen upon benchmark dose) divided by the estimated or measured human exposure level. The acceptability of a calculated MOE is a risk management decision, usually based upon a risk policy determined by the authoritative body or established in some regulatory mandate. So it is not appropriate in the context of the assessment we are reviewing to equate a modal uncertainty factor with a MOE presumed to be acceptable.

Leaving aside discussions of MOE, one could consider modifying a UF or other aspect of the risk assessment if there were good reason (i.e. data) to conclude that a "healthy worker" population would not include certain sensitive subgroups. For example, if one knew that no fetuses would be exposed in an occupational setting, one might want to depart from changes in fetal body weight as an enpoint of consideration. Note that this decision would be a very hard sell in a regulatory context. I would find it difficult to provide a reasonable rationale for modifying either UFHtk or UFHtd in the absence of specific data on the occupationally exposed population.

Expert 6

Not my expertise

Expert 3

I do not believe that it would be necessary to modify the uncertainty factors. The primary difference in the risk assessment for workers will be their exposures to BD, which are far higher than those for the general public. Assuming no susceptibility differences between someone who chose to work in a BD-affected industry and the general public, there should no difference in an applied uncertainty factor.

Expert 2

In general, I am in agreement as recommended In Round 3, a net uncertainty factor value (and margin of exposure) of 30 was identified for assessing the potential hazards for ovarian atrophy and fetal body weight changes for general population exposures to BD. However, as stated before a net uncertainty facor of 30 for both the adverse outcomes observed in rodents upon exposure to 1, 3-BD exposure is not likely to be accepted by the US EPA unless a clear arguments are made that female occupational workers , especially of reproductive age are not likely to be in the workforce in diiferent operations job categories directly or indirectly to 1, 3 BD exposures. In absence of this justification based on demographic data/information, an additional Uncertainty factor of 3, at a

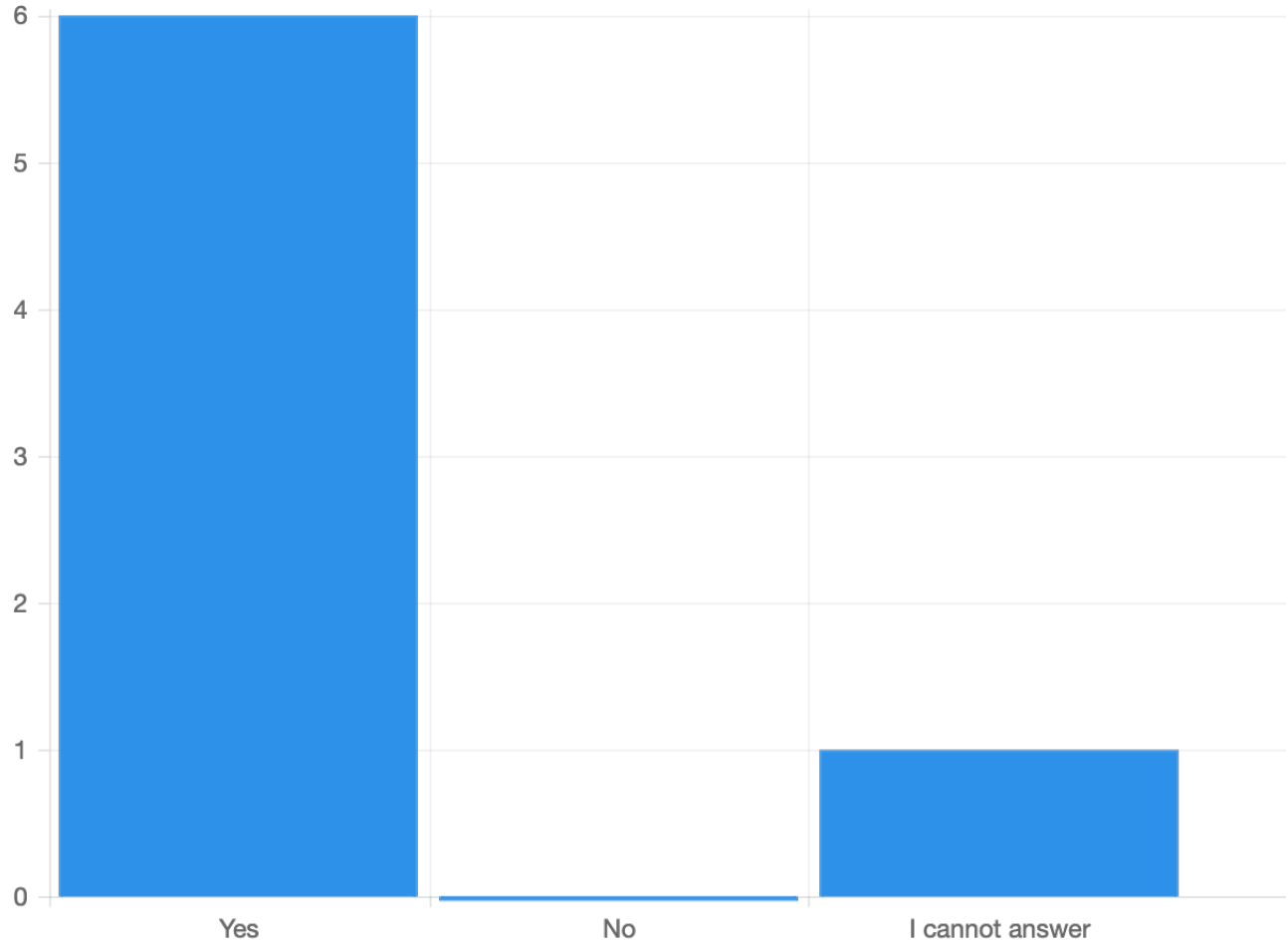
> **minimum may be applied with a net UFs value of 100.**

Expert 1

> I have no opinion on this matter.

Result 7.5 *(ID: 6417)*
Question 7.5 *(ID: 5810)*

Should the hemoglobin adduct data for butadiene metabolites in exposed workers (Section 4 of the Round 5 Summary Report) be used to quantify human variation in toxicokinetics for use in uncertainty factor and margin of exposure determination?



Legend

answers: 7
skips: 0

Answer Explanations

Expert 7 Explanation
Selected Answer(s): Yes

Based on the data presented, it is my opinion that the different Hb adducts are a reasonable way to quantify the variation in the TK for each of the 3 metabolites.

Expert 5 Explanation
Selected Answer(s): Yes

The data shown in Table 2 of the Round 5 Summary Report should be used for determining the kinetic portion of the uncertainty factor for human variation (UFh) from BD exposures based on the variation in human hemoglobin

adducts. The use of these study results for determining UFh is consistent with the EPA's application of data-derived extrapolation factors (USEPA, 2014).

Expert 4 Explanation
Selected Answer(s): Yes

I feel that these data should be used in calculation of a data-derived extrapolation factor to be used in lieu of a default UFHtk.

I was not convinced by the description of UF calculation in the Round 5 Summary Report. For example the fetal body weight changes UF = 3.2 x 3.2; was this to indicate that a default UFHtk is preferable to use of the hemoglobin adduct data?

Note also that I was not sold on the proposal to use the "green values" for ovarian atrophy and "yellow values" for fetal body weight changes. Before I read the text with this proposal and from my inspection of the calculations in table 2, I was about to propose using combined adduct data from both males and females. The Round 5 Report, provided insufficient rationale to limit the ovarian atrophy effect to DEB only.

I am answering the questions below using the green and yellow proposals, but I would require more explicit (even if repetitive) critieria for that decision.

Expert 6 Explanation
Selected Answer(s): Yes

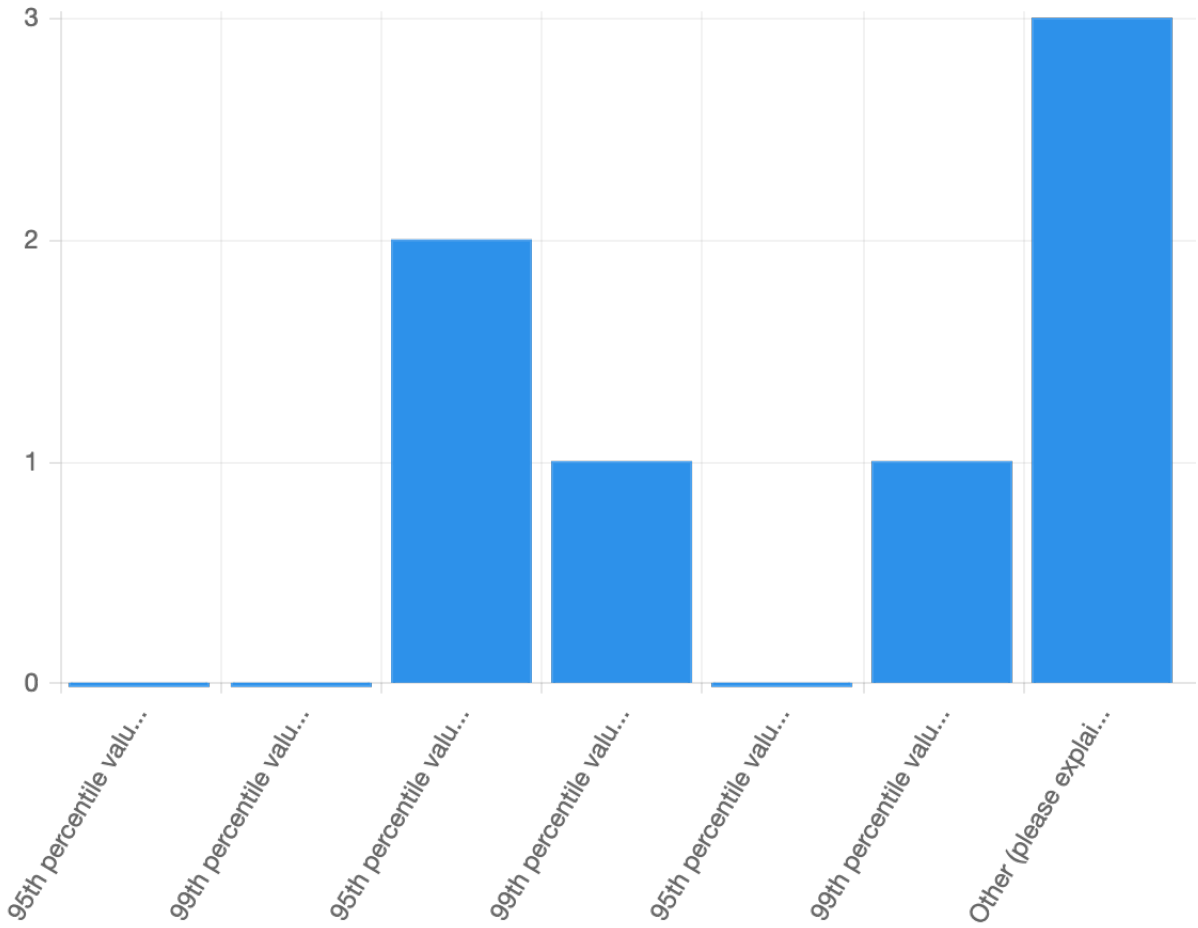
Yes the hemoglobin adduct and urine biomarkers are suitable to estimate variation in "BD exposure and and metabolism" and associate uncertainty .

Expert 1 Explanation
Selected Answer(s): Yes

I am sure that there is a way to use this data to refine exposure assessment and understand its limitations.

Result 7.6 *(ID: 6418)*
Question 7.6 *(ID: 5811)*

If you answered "Yes" to question 7.5, which value from Table 2 (hi-lighted in green) of the Round 5 Summary Report be used for protection of the ovarian atrophy effects of BD (attributed to metabolite DEB)?



Legend

95th percentile value for male workers from study 1 as reported in Boysen et al. (2022): 4.3: 0
99th percentile value for male workers from study 1 as reported in Boysen et al. (2022): 7.9: 0
95th percentile value for male and female workers from studies 1 and 2: 5.0: 2
99th percentile value for male and female workers from studies 1 and 2: 7.5: 1
95th percentile value for female workers from study 2: 3.8: 0
99th percentile value for female workers from study 2: 6.1: 1
Other (please explain): 3

answers: 7
skips: 0

Answer Explanations

Expert 7 Explanation
Selected Answer(s):
95th percentile value for male and female workers from studies 1 and 2: 5.0

In my opinion, the "5" UF for the 95th% seems very reasonable and health-protective.

Expert 5 Explanation
Selected Answer(s):
95th percentile value for male and female workers from studies 1 and 2: 5.0

For ovarian atrophy, DEB is the most important contributor to toxicity, and the hemoglobin adduct data on pyr-val reflects the internal dose of DEB. Thus, TSCA should use the pyr-val adduct percentile data from Table 2 of the Round 5 Summary Report for determining the kinetic portion of the uncertainty factor for human variation (UFh) from BD exposures. I favor the 95th percentile value of 5.0 from the combined male and female workers from studies 1 and 2 analyzed together for this purpose. The 95th percentile, rather than something lower, is a good choice of a conservative value and better than a 99th percentile value which can sometimes be distorted by outliers in the data and capture worst-case scenarios. I also favor the combined dataset from studies 1 and 2 because the dataset is larger and recently updated. Also, although ovarian atrophy is an effect only observed in female animals, other reproductive/developmental effects, like fetal body weight changes, were also seen in males, so I would choose the combined dataset on males and females for this uncertainty factor derivation.

Expert 4 Explanation
Selected Answer(s):
99th percentile value for male and female workers from studies 1 and 2: 7.5

A reference concentration (per US EPA) is designed to apply to the general US population including sensitive subpopulations. It does not apply only to the gender for which an adverse outcome has been identified, but rather is intended to be protective of all adverse outcomes in all genders. Thus if I were using the "green data" I would propose the information from the combined male and female workers used. That is, apply a UFHtk of 6.1 and a default UFHtd of 3.2 for a total UFH of 20.

Expert 6 Explanation
Selected Answer(s): Other (please explain)

This is very tricky question and we may be splitting hairs. Let's look at the 99th percentile. What we are missing is the 99th percentile value for male workers from study 2. Should there be a sex difference in variation one would expect the 99th percentile for male form study 2 to be close to 8.0, which is different than the 6.1 obtain for females. An import fact is the difference in group size and exposure range that may have affected the variation. When we can established a significant higher variation in males compared to females we may want to use the females only the ovarian atrophy effects of BD. If not we may want o chore the 99th percentile value for male workers from study 1 as reported in Boysen et al. (2022): 7.9, because it is derived form largest study with wide exposure range.

Expert 3 Explanation
Selected Answer(s): Other (please explain)

This question is beyond my area of expertise.

Expert 2 Explanation
Selected Answer(s): 99th percentile value for female workers from study 2: 6.1

I agree with the application of uncertainty factor of 10 for intra- human variation can be considered to be comprised of eual components (-3.2half -log values for each) for toxicockinetic and toxicodynamic variations . The 99th percentile value based on adducts in female workers from Study 2 for both enpoints of toxicity (ovarian atrophy and body weight changes) in rodents, the uncertainty factor values as calculated 20 for ovarian atrophy and 10 for body weight changes could be selcted.

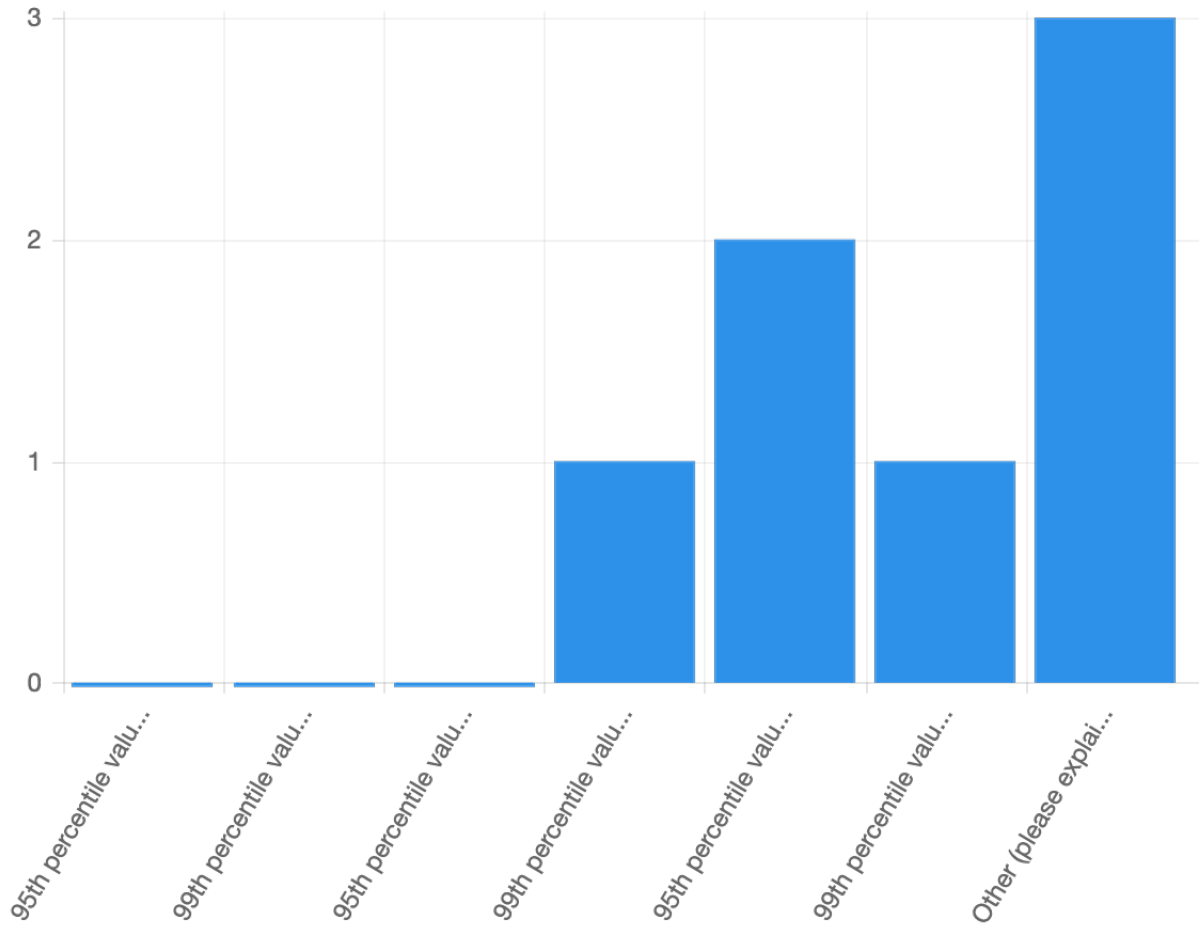
Expert 1 Explanation

Selected Answer(s): Other (please explain)

I have no idea how my answer to 7.5 relates to 7.6, sorry.

Result 7.7 *(ID: 6419)*
Question 7.7 *(ID: 5812)*

If you answered "Yes" to the question 7.5, which value from Table 2 (hi-lighted in yellow) of the Round 5 Summary Report be used for protection of the fetal body weight effects of BD (attributed to all three epoxide metabolites)?



Legend

95th percentile value for male workers from study 1: 3.4: 0
99th percentile value for male workers from study 1 : 4.5: 0
95th percentile value for female workers from study 2: 2.2: 0
99th percentile value for female workers from study 2: 3.2: 1
95th percentile value for male and female workers from studies 1 and 2: 2.9: 2
99th percentile value for male and female workers from studies 1 and 2: 4.2: 1
Other (please explain): 3

answers: 7
skips: 0

Answer Explanations

Expert 7 Explanation
Selected Answer(s):
95th percentile value for male and female workers from studies 1 and 2: 2.9

I would use that but round to "3".

Expert 5 Explanation
Selected Answer(s):
95th percentile value for male and female workers from studies 1 and 2: 2.9

For fetal body weight effects, DEB, EB and EBD are all thought to contribute to toxicity, and the hemoglobin adduct data on pyr-val, HB-val, and THB-val reflect their internal doses, respectively. Thus, TSCA should use the percentile data for the combined adducts from Table 2 of the Round 5 Summary Report for determining the kinetic portion of the uncertainty factor for human variation (UFh) from BD exposures. I favor the 95th percentile value of 2.9 from the combined male and female workers from studies 1 and 2 analyzed together for this purpose. The 95th percentile, rather than something lower, is a good choice of a conservative value and better than a 99th percentile value which can sometimes be distorted by outliers in the data and capture worst-case scenarios. I also favor the combined dataset from studies 1 and 2 because the dataset is larger and recently updated. Finally, fetal body weight changes were observed in both sexes, so I would choose the combined dataset on males and females for this uncertainty factor derivation.

Expert 4 Explanation
Selected Answer(s):
99th percentile value for male and female workers from studies 1 and 2: 4.2

A reference concentration (per US EPA) is designed to apply to the general US population including sensitive subpopulations. It does not apply only to the gender for which an adverse outcome has been identified, but rather is intended to be protective of all adverse outcomes in all genders. Thus if I were using the "yellow data" I would propose using the information from the combined male and female workers. That is, apply a UFHtk of 4.2 and a default UFHtd of 3.2 for a total UFH of 10.

And as usual, I do not equate women of childbearing age with fetuses.

Expert 6 Explanation
Selected Answer(s): Other (please explain)

This is very tricky question and we may be splitting hairs. Let's look at the 99th percentile. What we are missing is the 99th percentile value for male workers from study 2. Should there be a sex difference in variation one would expect the 99th percentile for male form study 2 to be close to 8.0, which is different than the 6.1 obtain for females. An import fact is the difference in group size and exposure range that may have affected the variation. When we can established a significant higher variation in males compared to females we may want to use the females only the ovarian atrophy effects of BD. If not we may want o chore the 99th percentile value for male workers from study 1 as reported in Boysen et al. (2022): 7.9, because it is derived form largest study with wide exposure range.

Expert 3 Explanation
Selected Answer(s): Other (please explain)

This question is beyond my area of expertise.

Expert 2 Explanation

Selected Answer(s): 99th percentile value for female workers from study 2: 3.2

For the fetal body weight effects, the 99 percentile value of female workers from the Study 2 is 3.2 and is appropriate.

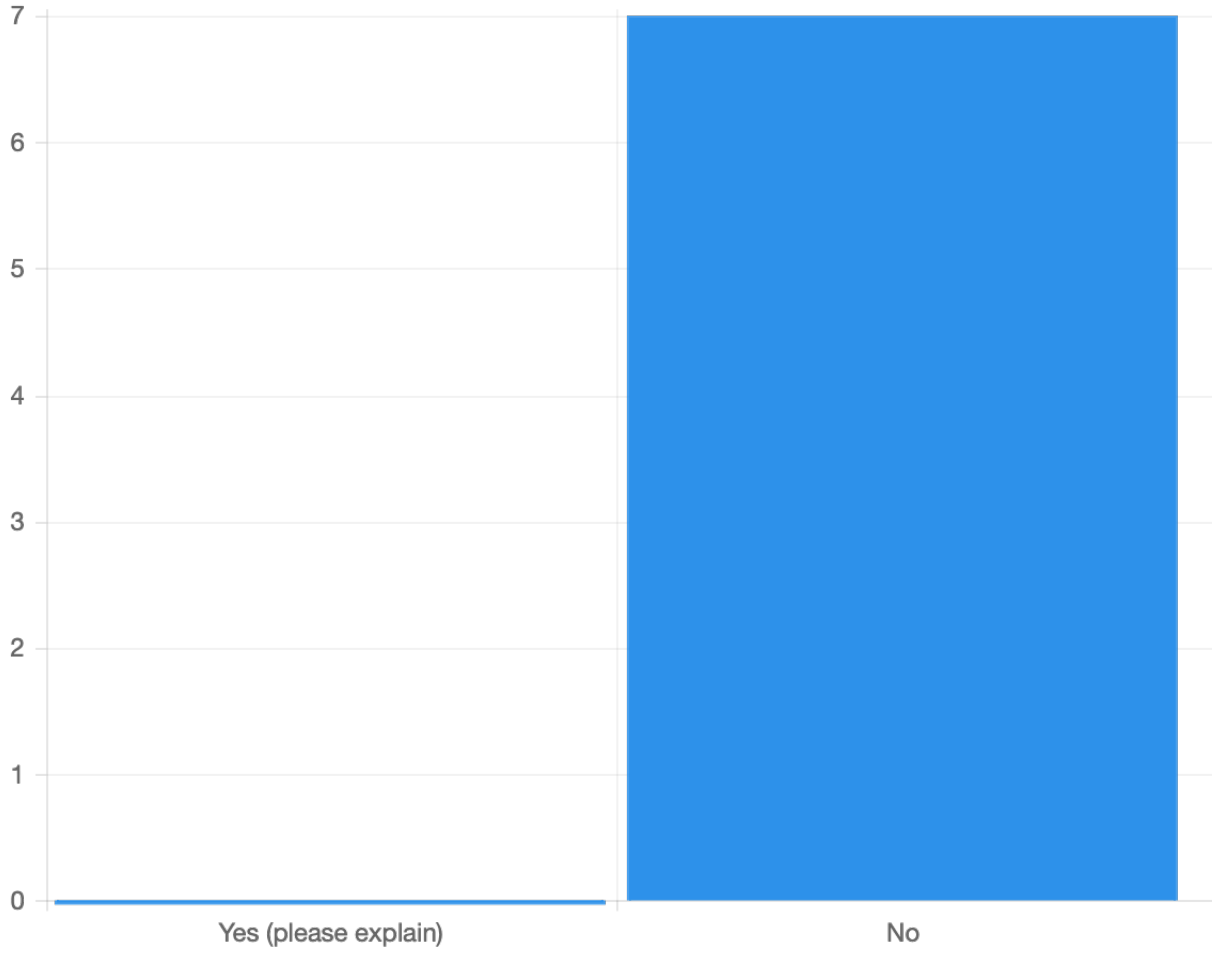
Expert 1 Explanation

Selected Answer(s): Other (please explain)

I have no idea how my answer to 7.5 relates to 7.7, sorry.

Result 7.8 *(ID: 6420)*
Question 7.8 *(ID: 5813)*

Are you aware of additional data for respiratory protection factors that should be considered in Section 5 of the Round 5 Summary Report?



Legend

answers: 7
skips: 0

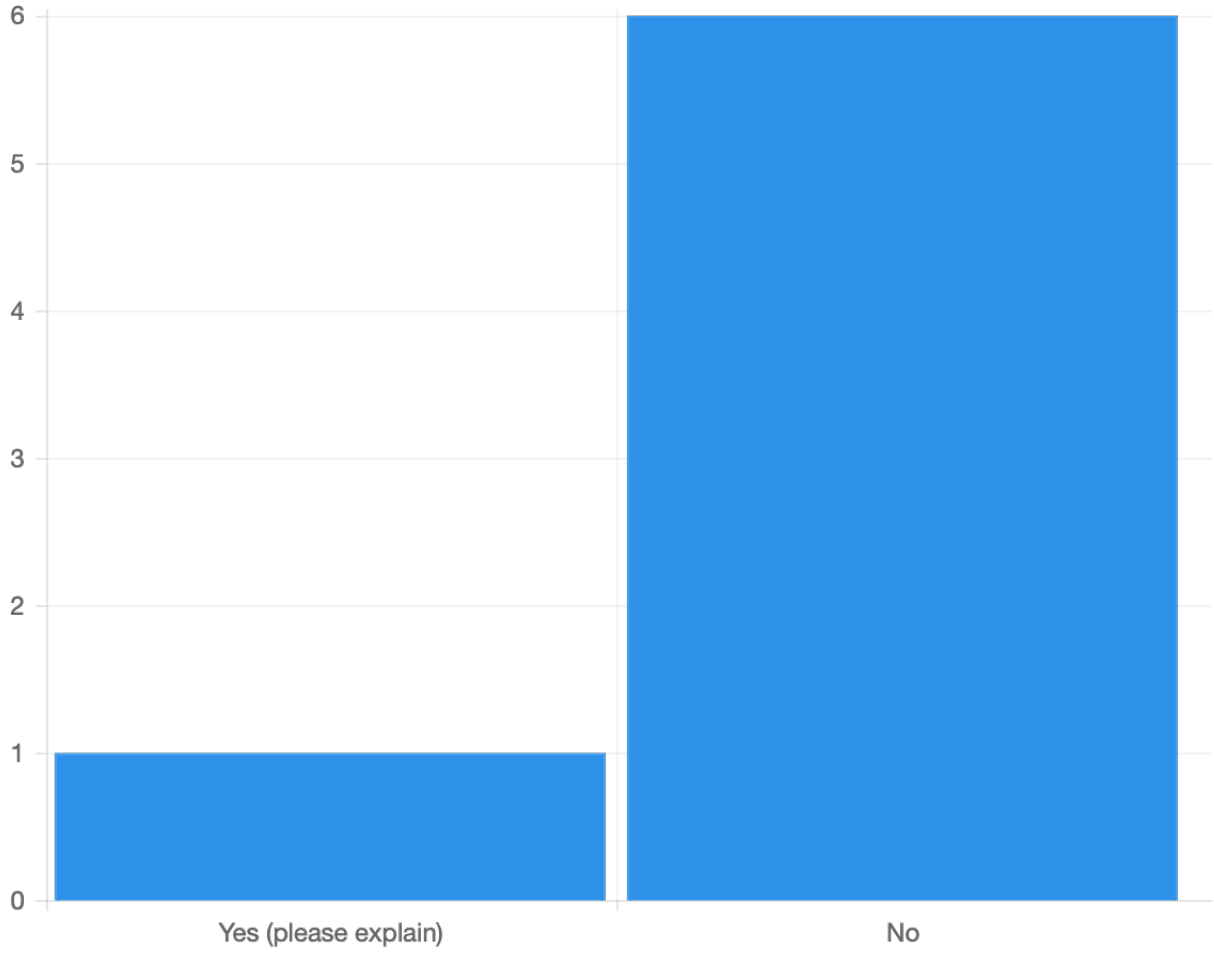
Answer Explanations

Expert 5 Explanation
Selected Answer(s): No

I have very limited experience with exposure modeling, therefore, I have no suggestions for additional data for respiratory protection factors.

Result 7.9 *(ID: 6421)*
Question 7.9 *(ID: 5814)*

Do you have any suggestions to refine or revise the cumulative probability density functions defined for the respirator protection factors (Figure 4)?



Legend

answers: 7
skips: 0

Answer Explanations

Expert 5 Explanation
Selected Answer(s): Yes (please explain)

I don't understand the concave, step-function shape of the cumulative probability density function for WPF values for the half-mask respirators shown in Figure 4 with a 5th percentile of ~1000. This is quite different from Figure 3 which shows smooth s-shaped curves for the cumulative probability density function for WPF values for the half-mask respirators with a 5th percentile of ~12.5. Both Figures appear to be based on the same datasets (Cohen et al. 1984; Galvin et al. 1990; Weber and Mullins, 2000), so it is unclear what these differences are between them.

Expert 6 Explanation
Selected Answer(s): No

Not my expertise.

Expert 2 Explanation
Selected Answer(s): No

None.

Appendix C: Supplemental Information for 1,3-Butadiene (BD) Hazard Assessment

1. Proposed Modes of Action (MOA) for Key Noncancer Effects of 1,3-Butadiene (BD)

The critical noncancer endpoints for 1,3-butadiene (BD) risk assessment include its effects on ovarian atrophy and decreases in fetal body weights in mice. These endpoints have been used by many regulatory agencies to support noncancer risk assessment of BD over the past few decades (see Table 1 of Kirman et al., 2022). As part of SciPinion's problem formulation, we recognized ATSDR's conclusion to not derive minimal risk levels for BD "*due to the large species differences in the metabolism of 1,3-butadiene and the lack of chemical-specific data to adjust for these differences, which may result in the MRL overestimating the risk to humans*" (ATSDR, 2012). To support interspecies extrapolations in the noncancer risk assessment for these endpoints we relied upon data-derived extrapolation factor (DDEF) values (USEPA, 2014) based upon methods and toxicokinetic data that became available for BD after ATSDR's publication. Under USEPA's DDEF guidelines, "*Information on MOA is important in DDEF derivation, even when a complete understanding of the mechanism is not available*". To support the application of DDEFs in the human risk assessment for BD, EPA has requested a characterization of the key events in the proposed MOA for the key noncancer endpoints. The text below provides a summary of MOA information for both endpoints to support DDEF application.

1.1 Proposed MOA for Ovarian Atrophy

The section below provides a brief description of the Key Events (KEs) in the proposed MOA for ovarian atrophy in rodents, the weight of evidence supporting the MOA in rodents within the context of the modified Bradford-Hill criteria, an assessment of human relevance, and the DDEF value used to support the noncancer risk assessment.

1.1.1 Key Events

Metabolism is an important determinant of BD's toxicity. BD itself is considered to be biologically inert (i.e., it does not bind to cellular macromolecules or to receptors). Instead, BD is metabolized to multiple reactive epoxide metabolites to which the toxicity of BD is attributed. A large body of evidence that includes *in vitro, in situ*, and *in vivo* studies supports the presence of large species differences in the metabolic activation of BD (mice>rats>humans), which in turn are expected to underly species differences in BD's toxic potency. Because of the importance of metabolism, the definition of MOA has been extended here to specifically include toxicokinetic events in addition to toxicodynamic events.

- *KE1: Metabolism of BD to 1,2,3,4-Diepoxybutane (DEB)* - BD is initially oxidized to the 1,2-epoxy-3-butene (EB), a reaction mediated primarily by P450 isozyme CYP2E1 although other isozymes such as CYP2A6 have also been shown to be involved. Further oxidation of EB by P450 produces the DEB that has been shown to be the causative agent for ovarian toxicity (Doerr et al., 1995, 1996). DEB has been detected in animal

tissues *in vivo, in situ* (Filser et al., 2001, 2010), and *in vitro* (Seaton et al., 1995; Motwani and Tornqvist, 2014). pyr-Val adducts, a specific biomarker that forms as a result of a reaction between DEB and hemoglobin, has been detected in rats and mice (Swenberg et al., 2007; Georgieva et al., 2010). Large species differences (mice>rat>human) have been quantified for the internal doses of DEB (based on measured pyr-Val adducts) following exposures to BD (Motwani and Tornqvist, 2014). Local tissue metabolism of BD in rodent ovary is not expected based upon data collected for a structurally similar chemical (4-vinylcyclohexene or VCH, which is a dimer of BD) that produces the same effects on mouse ovary due to diepoxide metabolite formation (Doerr et al., 1995, 1996). Specifically, rat and mouse ovaries did not have detectable capacity to metabolize VCH to its diepoxide (VCD) (Keller et al., 1997).

- *KE2: Distribution of DEB to Ovary* – Wide distribution of DEB has been reported based on direct measurements in multiple tissues, including ovary, in rats and mice (Thornton-Manning et al., 1995, 1997, 1998; Himmelstein et al. 1995).
- *KE3: Apoptosis, Oxidative Stress, Altered Gene Expression* – By analogy to a structural analog, VCD, diepoxides like DEB cause apoptotic cell death in primary and primordial follicles. Although the precise mechanism for diepoxides is not clear, it appears to involve oxidative stress, altered signaling pathways, and altered gene expression (Zhou et al., 2023; Liu et al., 2015, 2023; Li et al. 2014; Kappeler and Hoyer, 2012; Halicioglu et al., 2021; Abolaji et al., 2016).
- *KE4: Destruction of Primary and Primordial Ovarian Follicles* – Destruction of primary and primordial ovarian follicles has been observed in mice exposed directly to DEB and a DEB precursor (EB), and in rats exposed to DEB but not in rats exposed to EB (Doerr et al., 1995, 1996).
- *KE5: Premature Ovarian Failure* – Premature ovarian failure (i.e., ovarian atrophy; early onset menopause) has been observed in mice exposed to BD (NTP, 1984, 1993; Bevan et al., 1996), but not in rats exposed to much higher concentrations (Owen et al., 1987; Bevan et al., 1996).

1.1.2 MOA Weight of Evidence Using Modified Bradford-Hill Criteria

Dose Response Relationships

Mice exposed to BD developed ovarian atrophy (NTP, 1993, 1984; Bevan et al. 1996), but rats exposed to higher concentrations of BD did not develop this effect (Bevan et al. 1986; Owen, 1987; Marty et al. 2021). There are large species differences in the threshold for BD in producing ovarian atrophy:

- In mice, the threshold for ovarian atrophy has been shown to be dependent on air concentration and exposure duration (NTP, 1993):
    - 40 weeks: NOAEL = 62.5 ppm, LOAEL = 200 ppm
    - 65 weeks: NOAEL = 6.25 ppm, LOAEL = 62.5 ppm
    - 104 weeks: NOAEL <6.25 ppm, LOAEL = 6.25 ppm
- In contrast, the NOAEL for rats exposed to BD for 104 weeks is more than 1000-fold higher than the corresponding value for mice (>8,000 ppm; Owen et al., 1987). A

complete table of dose-response and the incidence data for both species is provided below (see **Table 2** below).

- Based on current understanding of species differences in metabolic activation of BD and internal dose estimates of DEB based upon hemoglobin biomarkers (Motwani and Tornqvist, 2014), the NOAEL for ovarian atrophy in humans is expected to be higher than the corresponding NOAEL value identified for rats.

Temporal Association

Toxicokinetic events (KEs 1-2) have been demonstrated in rodents following acute exposures to BD (Thornton-Manning et al. 1997,1998). Most of the mechanistic studies conducted for structural analog, VCD, have demonstrated effects on apoptosis, oxidative stress, and altered signaling and gene expression (KE 3) following short-term exposures (Zhou et al., 2023; Liu et al., 2015, 2023; Li et al. 2014; Kappeler and Hoyer, 2012; Halicioglu et al., 2021; Abolaji et al., 2016). Follicle cell depletion has been observed in mice following short-term exposures (30-day) to EB and DEB, and in rats following short-term exposures to DEB (Doerr et al., 1996), which is well before the observations for ovarian effects in mice (NTP, 1993). As such the available evidence is temporally consistent with ovarian effects observed in mice exposed for subchronic and chronic durations. In addition, as noted above (see Dose Response Relationships), there is a clear duration dependence for the ovarian atrophy threshold in mice (NTP, 1993).

Strength, Consistency, and Specificity

Ovarian toxicity is consistently observed in mice exposed to BD (Doerr et al., 1996; NTP, 1984, 1993; Bevan et al., 1996), and consistently absent in rats exposed to BD (Doerr et al., 1996; Owen et al., 1987; Bevan et al., 1996). The proposed MOA is consistent with observed species differences in the metabolic activation of BD to a diepoxide intermediate (mouse>rat; Filser et al., 2001, 2007, 2010; Thornton-Manning et al., 1995a,b; Motwani and Tornqvist, 2014) and sensitivity to ovarian effects (mouse>rat; Doerr et al., 1996; NTP, 1984, 1993; Bevan et al., 1996; Owen et al., 1987).

There are marked species differences in effects observed between rats, which do not exhibit BD-induced ovarian atrophy following chronic exposures as high as 8,000 ppm (Owen et al., 1987), and mice, which exhibit BD-induced ovarian atrophy following chronic exposures as low as 6.25 ppm BD (NTP, 1993). Furthermore, the mono-epoxide metabolite of BD, EB, has been shown to be toxic to mouse ovary but not to rat ovary, reflecting greater conversion of EB to DEB in mice. Direct exposure to DEB was toxic to the ovary of both species, albeit with a lower efficacy in rats than in mice (Doerr et al., 1996).

Species differences in ovarian effects (mouse>rat) also correlate well with species differences in the internal doses of DEB (mouse > rat), as reported in *in vitro* studies (Csanady et al., 1993; Schmidt and Loeser, 1985; Krause and Elfarra, 1997; Bond et al., 1993; Kreuzer et al., 1991; Seaton et al., 1995), in situ studies (Filser et al., 2001, 2010), and *in vivo* studies (Filser et al., 2007; Thornton-Manning et al., 1995). Quantitative differences in the *in vivo* production of BD metabolites are also reflected in their *in vivo* accumulations as hemoglobin adducts. A DEB-specific hemoglobin adduct, N,N-(2,3-dihydroxy-1,4-butadiyl)-valine (pyr-Val), has been identified

and measured, providing insights into species and exposure differences in BD metabolism (Boysen et al., 2004, 2012). The formation of pyr-Val hemoglobin adducts has been studied in male and female mice and rats exposed to 1.0 ppm by inhalation for 6 hours/day for four weeks (Swenberg et al., 2007), in which adduct burdens (i.e., concentrations in blood due to cumulative exposure) in rats were more than 30-fold lower than the corresponding values in mice. Additionally, the formation of pyr-Val adducts in rats and mice of both sexes was assessed following 4-week exposures to either 1, 6.25, or 62.5 ppm BD for 6 hours/day (Georgieva et al., 2010). The difference between species was dose-dependent, with a larger difference observed at higher concentration compared to low concentrations. A less pronounced difference between species was also reported by these authors following 2-week exposures to BD, primarily because in the mouse the 2-week adduct burdens were appreciably lower than observed at 4 weeks, suggesting that steady-state had not been reached. Humans have been shown to form even less of the DEB than rats (Boysen et al., 2012; see Figure 1 of Motwani and Tornqvist, 2014).

Biological Plausibility and Coherence

There is strong evidence that ovarian atrophy is mediated by the formation of diepoxides, such as the BD diepoxide metabolite DEB (Doerr et al., 1995; 1996) and the diepoxide of VCH (VCD). Ovarian toxicity was observed following exposure to diepoxides (DEB, vinylcyclohexene diepoxide) and diepoxide precursors (EB, BD dimer or vinylcyclohexene, vinylcyclohexene epoxide, isoprene), but absent following exposure to structural analogues that do not form diepoxides (ethylcyclohexene oxide, vinylcyclohexane oxide, cyclohexene oxide) (Doerr et al. 1995, 1996). Although the molecular mechanism is not fully understood, diepoxides appear to selectively destroy the primordial and primary follicles via apoptosis, thereby accelerating the normal process of atresia (Springer et al., 1996; Hoyer and Sipes, 2007). Accelerated oocyte depletion leads eventually to premature ovarian failure and cessation of the estrous cycle.

Other MOAs

No other MOAs are proposed for the effects of BD on ovarian atrophy.

Uncertainties, Inconsistencies, Data Gaps

Uncertainties, inconsistencies, and data gaps on some aspects of the MOA are discussed below.

- *Uncertainty Associated with Recently Proposed Metabolite* - Researchers have recently proposed the potential formation of additional bifunctional metabolites for BD, including the formation of a chlorinated metabolite via myeloperoxidase and hypochlorous acid (Elfarra and Zhang, 2012; Wang et al., 2018; Wu et al., 2019) and ketone/aldehyde metabolites of EBD via alcohol dehydrogenase in isogenic chicken cells *in vitro* (Nakamura et al., 2021). The formation of these metabolites *in vivo* following exposure to BD, as well as the ability of these hypothesized bifunctional metabolites to cause ovarian atrophy has not been demonstrated (i.e., a role for these potential metabolites in the effects BD is in the hypothesis stage at present). If future research shows these metabolites to be important to both internal dose and to contribute to ovarian atrophy, the relative potency approach used for the assessment of fetal body weight changes (see below) could be extended and applied to include contributions from additional metabolites for ovarian atrophy.

- *Uncertainty in the Toxicodynamic Differences Between Mice and Rats in Sensitivity to DEB* – As noted above, NOAEL values for ovarian atrophy following lifetime exposures to mice and rats differ by more than 1,280-fold (>8000 ppm in rats vs. <6.25 ppm in mice). However, species differences in blood AUC between these species are only approximately 18.6-fold (27 vs 1.45 nmol*hr/ppm for female mice and rats, respectively; Motwani and Tornqvist, 2014), suggesting a toxicodynamic difference between these species more than 69-fold (1280/18.6) for lifetime exposures to BD. Based on a benchmark dose (BMD) analysis of the short-term study data of Doerr et al. (1996) in which rats and mice were directly exposed to DEB for 30 days, rats were estimated to be approximately 11-fold less sensitive than mice to the effects of DEB due to toxicodynamic differences (DDEF for toxicodynamic differences of 0.088; Kirman et al. 2022). The DDEF of 0.088 for toxicodynamics differences between mice and rats was applied to rat test concentrations to support BMD analyses of mouse and rat data combined (i.e., rat dose-response data were expressed in terms of mouse sensitivity to DEB by shifting them to the left by a factor of approximately 11). There is considerable uncertainty in the DDEF value derived from short-term data and applied to account for toxicodynamic differences between mice and rats following long-term exposures (i.e., these differences may be considerably higher than 11-fold used in the noncancer assessment).
- *Data Gap for DEB Dosimetry in Women* – For the purposes of performing interspecies extrapolation, internal dose estimates for DEB (blood AUC) were used based upon the assessment of Motwani and Tornqvist (2014). In this study, the authors relied upon biomarkers (pyr-Val hemoglobin adducts) collected in exposed male workers (Albertini et al., 2003; Boysen et al. 2012). There is some uncertainty in applying the internal dose estimates from male workers to the assessment of endpoints that are specific to females (i.e., ovarian atrophy, fetal body weight changes). We have recently been provided access (with permission from Drs. Albertini and Boysen) to some unpublished data that includes measurements in BD-exposed female workers (collected as part of Vacek et al. 2010, and then later analyzed after refined methods for DEB detection were developed). Preliminary assessment of these data indicate that the use data collected from male workers for quantifying species differences is conservative since DEB biomarker levels in females is lower than corresponding values in males for a given exposure to BD. A preliminary assessment of these data is included as an **Appendix A**, and a separate publication for these unpublished biomarker data by Dr. Boysen is anticipated in the near future (Dr. Boysen has expressed interest in getting these data published separately).

1.1.3 Human Relevance of MOA

Based upon this evaluation, the key questions identified for evaluating the human relevance of the MOA (Boobis et al., 2008; Meek et al. 2014) are addressed as follows:

- *Is the weight of evidence sufficient to establish a mode of action in animals?*

Yes: The MOA for ovarian toxicity in animals exposed to BD, through the formation of a diepoxide metabolite (DEB), is well supported by available literature.

- *Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?*

  No: Ovarian toxicity is observed when rats are exposed directly to DEB (Doerr et al. 1995, 1996), indicating that this endpoint is not specific to mice. Data from structural analog, VCD lend additional support to this conclusion. Like DEB, structural analog VCD also produces ovarian toxicity in rats following direct administration. Additionally, ovarian toxicity was observed in nonhuman primates exposed to VCD via intramuscular injection or surgical implantation of a degradable fiber (Appt et al., 2006, 2010). Lastly, *in vitro* studies show that VCD produces increased intracellular ROS, DNA damage, and altered the expression of genes related to apoptosis and oxidative stress, resulting in increased apoptosis in human ovarian (granulosa) cells (Song et al., 2023). Together, the weight of evidence supports a conclusion that qualitatively the endpoint of rodent ovarian toxicity is relevant to human health.

- *Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans?*

  Possibly, but relevance is assumed at this time: There are profound quantitative differences between mice, rats, and humans with respect to circulating levels of DEB following exposure to BD, which need to be considered in risk assessment. Studies of hemoglobin biomarkers (Swenberg et al., 2011; Boysen et al., 2012; Motwani and Tornqvist, 2014) demonstrate that for a given exposure to BD, estimated DEB blood levels in humans are several orders of magnitude lower than corresponding DEB blood levels in mice (see Table 3 of Motwani and Tornqvist, 2014). Due to these species differences, some of the human equivalent concentration (HEC) values calculated for corresponding test concentrations in mouse studies exceed $1x10^5$ ppm, levels at which BD's explosivity and potential for oxygen displacement become of concern. It is possible that humans are not capable of producing levels of DEB that are sufficient to produce ovarian toxicity (i.e., above a threshold for this endpoint), but this hypothesis would require further evaluation. For the risk assessment in preparation, it is assumed that after accounting for species differences in the metabolic activation of BD, the ovarian effects observed in laboratory animals are relevant to human health.

1.1.4 Data-Derived Extrapolation Factor

To support the noncancer risk assessment for BD, we have derived the following DDEF values:

- *Interspecies Extrapolation for Toxicokinetic Differences (EFAK)* – For extrapolating from mice and rats to humans, respective DDEF values of 0.00087 and 0.0162 were calculated as described in Kirman et al. (2022) to account for differences in the internal dose for DEB (blood AUC) for a given exposure to BD. These values are based on the internal

dose estimates calculated by Motwani and Tornqvist (2014; see their Table 3) using pyr-Val biomarker measurements in all three species.

- *Intraspecies Variation in Toxicokinetic Factors (EFHK)* – Variation in pyr-Val biomarkers in exposed workers from published sources (Boysen et al., 2022) and unpublished sources (data provided by Drs. Boysen and Albertini) was used to quantify human variation in internal dose for DEB (blood AUC). Derived values ranged from 3.8 to 7.9 depending upon the data sets included (e.g., male, female, combined, published, unpublished) and the upper percentile considered (e.g., 95%, 99%). Additional detail will be provided in the risk assessment and in a future publication for these data. These values are slightly higher than the default value for human variation in toxicokinetics (i.e., ~3), and are consistent with human variation in THB-val adduct variation due to combinations of genetic polymorphisms in metabolizing enzymes (Fustinoni et al., 2002).

Confidence in the DDEF values and resulting human equivalent concentrations is considered high since they are derived from data collected in multiple studies, across all three species of interest (including a large number of exposed workers) and rely upon a biomarker (pyr-Val) that directly reflects the proposed causative agent (DEB) for ovarian atrophy observed in rodents.

1.2 Proposed MOA for Fetal Body Weight Effects

The section below provides a brief description of the Key Events (KEs) in the proposed MOA for fetal body weight changes in rodents, the weight of evidence supporting the MOA in rodents within the context of the modified Bradford-Hill criteria, an assessment of human relevance, and the DDEF value used to support the noncancer risk assessment.

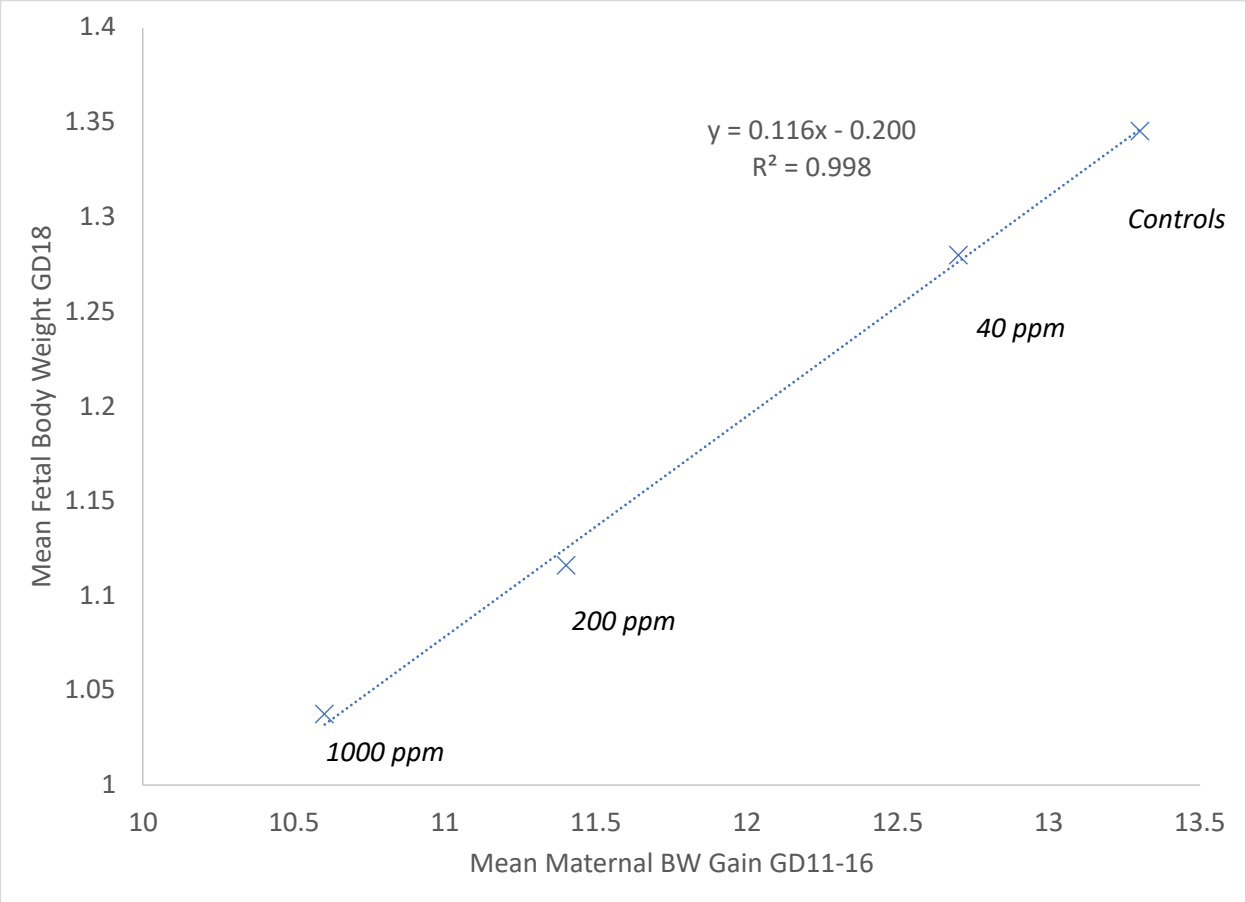
4.1.2.1 Key Events

Information on the MOA for the effects on BD exposure on fetal body weight in mice are limited. Key events (KEs) for BD's proposed MOA in fetal body weight in mice are summarized below. As noted above for the ovarian effects of BD, because metabolism is an important determinant of BD's toxicity, and because of the large species differences (mouse>rat>human) in the metabolic activation of BD to reactive metabolites, the definition of MOA has been extended to specifically include toxicokinetic events in addition to toxicodynamic events.

- *KE1: Metabolism of BD to Reactive and Toxic Epoxide metabolites* - BD is initially oxidized to the 1,2-epoxy-3-butene (EB), a reaction mediated primarily by P450 isozyme CYP2E1 although other isozymes such as CYP2A6 have also been shown to be involved. Further oxidation of EB by P450 produces the DEB that has been shown to be the causative agent for ovarian toxicity. DEB has been detected in animal tissues in vivo, in situ (Filser et al., 2001, 2010), and in vitro (Seaton et al., 1995; Motwani and Tornqvist, 2014). Hydrolysis of DEB yields 3,4-epoxybutane-1,2-diol (EBD). Hemoglobin adducts that reflect circulating blood levels of all three epoxide metabolites of BD have been characterized in mice, rats, and humans (Swenberg et al., 2007; Georgieva et al., 2010; Boysen et al., 2012) and have been used to quantify internal doses (AUC in blood) (Motwani and Tornqvist, 2014).

- *KE2: Distribution of Epoxide Metabolites to Maternal and Fetal Tissues* – Wide distribution of BD's metabolites has been reported based on direct measurements in multiple tissues, including uterus, in rats and mice (Thornton-Manning et al., 1995, 1997, 1998; Himmelstein et al. 1995). Distribution to placenta and fetal tissues is inferred based upon observations of wide distribution to other tissues.
- *KE3: General Toxicity Resulting in Reduced Maternal Body Weight Gain and Reduced Fetal Body Weight* – In mice, exposure to BD during gestation (GD 5-15) resulted in decreased maternal weight gain (on GD11-16) and decreased fetal body weights (Hackett et al., 1987a). In the original report, the lowest test concentration (40 ppm) was identified as a LOAEL for fetal body weight changes in males, whereas this exposure level was identified as a NOAEL for fetal body weight changes in females, and for maternal toxicity. A reanalysis of these data (Green, 2003; which also provide mean fetal body weight values and standard deviations with greater precision) to correct errors in the initial analysis resulted in a conclusion of 40 ppm identified as a NOAEL for fetal body weight changes in males as well. Inspection of the data for maternal body weight gain and fetal body weight changes (for males and females combined) indicates a high degree of correlation between these two endpoints (**Figure 2**). When expressed as a percentage of control values, these two dose-response trends are essentially identical (95% vs 96%, 86% vs 84%, 80% vs. 78% for low, mid, and high test groups, respectively. No information on feed intake was included in the initial report. For this reason, the effects of BD on maternal weight gain and fetal body weights are considered to reflect the general toxicity of BD to dam and fetus, which may or may not be accompanied by reduced feed consumption.

Figure 2. Maternal Body Weight Gain vs. Fetal Body Weights in Mice Exposed to BD (Hackett et al., 1987a)



1.2.2 MOA Weight of Evidence Using Modified Bradford-Hill Criteria

Dose Response Relationships

Exposure to BD produces decreases in fetal body weight in mice (Hackett et al. 1987a) but not in similarly exposed rats under identical test conditions (Hackett et al., 1987b):

- Mouse study (Hackett et al., 1987a; Green, 2003): NOAEL = 40 ppm; LOAEL = 200 ppm
- Rat study (Hackett et al. 1987b): NOAEL > 1000 ppm
- Based on current understanding of species differences in metabolic activation of BD and internal doses estimates of its epoxide metabolites based upon hemoglobin biomarkers (Motwani and Tornqvist, 2014), the NOAEL for fetal body weight changes in humans is expected to be even higher than the corresponding NOAEL value identified for rats.

Dose-response data are provided below (see **Table 1** below) for the effects of BD on fetal body weight.

Dose-response data are also available for BD metabolites supporting their role in body weight changes in non-pregnant animals:

- In mice receiving the mono-epoxide metabolite of BD (EB) via daily ip injections for 30 days, a 10% decrease in body weight was noted at the highest tested dose (1.43 mmol/kg-day; Doerr et al., 1996). In contrast, no significant change in body weights were noted in similarly exposed rats. These results are consistent with mice producing more DEB from EB than is produced in rats.
- In mice receiving diepoxide metabolite of BD (DEB) via daily ip injections for 30 days, a 15% decrease in body weight was noted at the highest dose tested (0.29 mmol/kg-day; Doerr et al., 1996). In rats, a 15% decrease in body weight was caused by a lower dose of DEB (0.14 mmol/kg-day; Doerr et al., 1996). Rats were more sensitive to the highest dose of DEB (0.29 mmol/kg-day) than mice, exhibiting a 50% decrease in body weight by day 25, with only 4/10 animals surviving until day 30.
- Together these results support a conclusion that the effect of BD on body weight gain and decreased body weight are attributable to its metabolites, and that the difference between rats and mice exposed to BD (Hackett et al., 1987a,b) reflect important toxicokinetic differences rather than toxicodynamic differences between species.

Temporal Association

Inspection of Figure 1 of Doerr et al. (1996) indicates that body weight changes are evident as soon as 5 days of exposure to EB or DEB, which is temporally consistent with the response of Hackett et al. (1987a) following 10 days of exposure to BD. *In vitro* exposure of mouse pre-implantation embryos to DEB (widely considered to be the most potently toxic metabolite of BD) for 24 hours was sufficient time to result in signs of embryotoxicity (Clerici et al., 1995), and as such is temporally consistent with observations of reduced maternal weight gain and fetal body weight towards the end of the gestation period. Other metabolites of BD have not been directly assessed with respect to their embryotoxic potential, and this potential is inferred here.

Strength, Consistency, and Specificity

The data from Doerr et al. (1996) provide strong support for the role of BD metabolites, particularly DEB, in causing body weight changes in mice. In addition, there is some evidence supporting a role for DEB in the fetotoxic endpoints of BD:

- DEB is specifically considered to be "*highly embryotoxic in preimplantation mouse embryos in vitro at micromolar concentrations*" (Clerici et al., 1995).
- When administered directly, DEB also produces fetotoxicity, including reduced growth and viability, in the nonresponsive species rats (Chi et al., 2002), suggesting that species differences in metabolite formation underly species differences to responsiveness for this endpoint, a conclusion that is consistent with that reached by Christian (1996). For this reason, fetal body weight changes are not considered to be specific to mice, and the internal doses of BD metabolites achieved in rats under the conditions of the study of Hackett et al. (1987b) were below those needed to elicit the responses observed in mice (Hackett et al., 1987a).
- Potential fetotoxicity of BD's other epoxide metabolites is inferred. Empirical support for this inference from improved dose-response concordance across species was reported in

Kirman et al. (2022; see Figure 5C, D) when adjustments were made to account for species differences in internal dose for BD metabolites.

Biological Plausibility and Coherence

Because the parent chemical BD is considered to be biologically inert (does not react with cellular macromolecules or receptors), its toxicity is generally attributed to the formation of reactive and toxic metabolites (i.e., EB, DEB, and/or EBD). In a review of the reproductive and developmental toxicity of BD, Christian (1996) stated that, "*Regardless of the strain used, mice were always affected by BD at lower doses than rats, an expected observation, based on well recognized differences in pharmacokinetic (PK) parameters in these two species.*" Specifically, mice have been shown to produce higher internal doses of the reactive epoxide metabolites of BD than corresponding internal doses in other species (e.g., rats, humans), as quantified in Motwani and Tornqvist (2014).

Other MOAs

Chi et al. (2002) proposed an MOA involving placental pituitary adenylate cyclase-activating polypeptide expression and matrix metalloproteinase activity. A potential role for other BD metabolites in this MOA has not been evaluated. Because DEB has received much of the focus for BD mechanistic research, there is little information on the role for other metabolites in contributing to fetotoxicity and reduced fetal body weights.

Uncertainties, Inconsistencies, Data Gaps

There are no data regarding the metabolism of BD in fetal tissues that might impact internal doses to the fetus. However, information of the ontogenesis of the enzymes (e.g., cytochrome P450) suggest that fetal metabolism of BD is negligible. Specifically, expression of most cytochrome P450 isozymes, including CYP2E1 which is important for BD metabolism, is absent in fetal tissues 2 days prior to birth in mice, with expression starting and then increasing shortly thereafter (Hart et al., 2009; Cui et al., 2012). Because the exposure period used by Hackett et al. (1987a,b) (GD5-15) occurs well before CYP expression become important in developing mice, fetal metabolism of BD is expected to be negligible during the exposure period. Instead, delivery of the toxic metabolites of BD is expected to be driven by maternal metabolism and partitioning, and therefore is expected to be proportionate to the internal dose of metabolites in maternal blood.

A role for other metabolites in fetal endpoints is plausible, but uncertain. In light of the limited information in the MOA for fetal body weight changes, consideration of a possible role of other metabolites, particularly for EBD (the primarily epoxide metabolite circulating in humans following BD exposure; Motwani and Tornqvist, 2014) is considered to be a conservative approach (i.e., health protective). Specifically, species adjustments based on DEB as the single causative agent would result in the derivation of higher reference concentration values for this endpoint than corresponding adjustments based on the combined contributions of DEB, EB, and EBD (by a factor of ~6.5 based on DDEF value of 0.00087 based on differences in DEB alone vs. DDEF value 0.00563 for all three epoxide metabolites combined; Kirman et al., 2022).

There is uncertainty in the key assumption that cytotoxic potency from *in vitro* studies can be used to quantify potency for reduced fetal body weights under a MOA involving general toxicity. It is assumed that the epoxide metabolites' ability to bind cellular macromolecules underlies cytotoxicity and general toxicity (as well as genotoxicity). This uncertainty will be explored further in the risk assessment through the application of Monte Carlo methods. The uncertainty associated with this assumption is preferable to alternatives of making no adjustments due to toxicokinetic differences, or to not deriving a noncancer value. For example, in 2012 (prior to the publication of Motwani and Tornqvist, 2014 methodology and the pyr-Val data in exposed workers from Boysen et al., 2012) ATSDR elected to not derive acute-,intermediate-, and chronic-duration inhalation minimal risk levels for BD due to the lack of chemical-specific data to adjust for the large species differences in metabolism may result in the MRL overestimating the risk to humans.

1.2.3 Human Relevance

Based upon this evaluation, the key questions identified for evaluating the human relevance of the MOA (Boobis et al., 2008; Meek et al., 2014) are addressed as follows:

- *Is the weight of evidence sufficient to establish a mode of action in animals?*

  Yes: There is evidence to support the importance of BD metabolism in MOA for producing fetal body weight changes, with some evidence supporting a specific role for DEB (Chi et al., 2002; Clerici et al., 1995; Doerr et al., 1996) and a plausible role proposed for other BD metabolites (including EB and EBD, the predominant epoxide metabolite BD estimated in humans).

- *Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?*

  No: Evidence of fetotoxicity including reduced fetal growth is observed when rats are administered DEB directly (Chi et al., 2002) and that DEB also reduces body weight in nonpregnant rats when administered directly (Doerr et al., 1996), Therefore this endpoint is not considered to be unique to mice exposed to BD, and fetal body weight changes are qualitatively assumed to be relevant to all mammalian species, including humans.

- *Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans?*

  No: There are clear quantitative differences between mice, rats, and humans with respect to circulating levels of epoxide metabolites following BD exposure, which need to be considered in BD risk assessment. Swenberg et al. (2010), Boysen et al. (2012), and Motwani and Tornqvist (2014) showed that for a given exposure to BD, BD metabolite levels in humans are lower than the levels in rats, which in turn are lower

than levels in mice. Therefore, it is assumed that after accounting for species differences in the metabolic activation of BD, the fetal body weight changes observed in laboratory animals are relevant to human health.

1.2.4 Data-Derived Extrapolation Factor

To support the noncancer risk assessment for BD, we have derived the following DDEF values:

- *Interspecies Extrapolation for Toxicokinetic Differences (EFAK)* – For extrapolating from mice and rats to humans, respective DDEF values of 0.0053 and 0.127 were calculated as described in Kirman et al. (2022). to account for differences in the internal doses and toxic potencies for all three epoxide metabolites (blood AUCs) for a given exposure to BD. These values are based on (1) the internal dose estimates calculated by Motwani and Tornqvist (2014; see their Table 3) using metabolite-specific biomarker measurements in all three species; and (2) metabolite-specific cytotoxic potencies.
- *Intraspecies Variation in Toxicokinetic Factors (EFHK)* – Variation in biomarkers in exposed workers from published sources (Boysen et al., 2022) and unpublished sources (data provided by Drs. Boysen and Albertini) was used to quantify human variation in internal doses (blood AUCs) for all three epoxide metabolites. Derived values ranged from 2.2 to 4.5 depending upon the data sets included (e.g., male, female, combined, published, unpublished) and the upper percentile considered (e.g., 95%, 99%). Additional detail will be provided in the risk assessment and in a future publication for these data. These values are generally consistent with default value for human variation in toxicokinetics (i.e., ~3), and are also consistent with human variation in THB-val adduct variation due to combinations of genetic polymorphisms in metabolizing enzymes (Fustinoni et al., 2002).

Confidence in the DDEF values and resulting human equivalent concentrations is considered high since they are derived from data collected in multiple studies, across all three species of interest (including a large number of exposed workers), and rely upon a metabolite-specific biomarkers that reflect the toxic metabolites of BD.

2. Calculation Details

2.1 Calculations for Dose-Response Assessment of Fetal Body Weight Changes

Dose-response data used to derive reference concentration values for BD based on fetal body weight changes are summarized in **Table 1**.

Table 1. Dose-Response Data Used to Assess Fetal Body Weight Changes in Mice and Rats Exposed to BD

	BD Exposure			BD Response Data for Fetal Body Weight		
Species (Reference)	**ppm, as tested (6 hours/day, GD 5-15)**	**Step 1: ppm, Continuous**	**Step 2: ppm, Human Equivalent Concentration**	**n**	**Mean (g)**	**SD (g)**

Mouse (Hackett et al. 1987a; Green, 2003)	0.0E+00	0.0E+00	0.0E+00	18	1.35	0.119
	4.0E+01	1.0E+01	1.8E+03	19	1.283	0.057
	2.0E+02	5.0E+01	8.9E+03	21	1.126	0.096
	1.0E+03	2.5E+02	4.4E+04	20	1.038	0.112
Rat (Hackett et al. 1987b)	0.0E+00	0.0E+00	0.0E+00	28	3.49	0.212
	4.0E+01	1.0E+01	7.9E+01	24	3.44	0.245
	2.0E+02	5.0E+01	3.9E+02	26	3.4	0.255
	1.0E+03	2.5E+02	2.0E+03	27	3.5	0.312

Calculations used to calculate human equivalent concentrations used in benchmark dose modeling efforts are described below.

- *Step 1*: In Column 3 in **Table 1**, continuous exposure values were calculated by multiplying the tested concentration values (in Column 2) by a factor of 0.25 (6 hours/24 hours)
- *Step 2*: In Column 4, human equivalent concentrations were calculated by dividing the continuous concentration values (in Column 3) by DDEF values of 0.00563 for mice or 0.127 for rats to account for species differences in internal doses for the epoxide metabolites of BD (EB, DEB, EBD) based upon the proposed MOA described above. Please see Kirman et al. (2022) for the specific data used to derive the DDEF values.
- *Step 3*: Continuous models within USEPA's BMDS program were then fit to the data in Columns 4 through 7 (shaded in yellow): (1) for mouse runs, only the data in Rows 3-6 are used; (2) for combined runs, the data in Rows 3-10 were used. The hi-lited data in **Table 1** can readily be copy and pasted into USEPA's BMDS spreadsheet program for the purposes of rerunning any dose-response models.

2.2 Calculations for Dose-Response Assessment of Ovarian Atrophy

Dose-response data used to derive reference concentration values for BD based on fetal body weight changes are summarized in **Table 2**.

Table 2. Dose-Response Data Used to Assess Ovarian Atrophy in Mice and Rats Exposed to BD

		BD Exposure				Response
Species	**Exposure Duration, weeks (Reference)**	**ppm, as tested (6 hours/day, 5 days/ week)**	**Step 1: ppm, Continuous**	**Step 2: ppm, Human Equivalent Concentration**	**Step 3: Adjustments to Express Rat Values in Terms of Mouse Sensitivity (toxicodynamic differences)**	**Incidence Ovarian Atrophy**
Mouse	104 (NTP, 1993)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	4/49
		6.25E+00	1.12E+00	1.28E+03	1.28E+03	19/49
		2.00E+01	3.57E+00	4.11E+03	4.11E+03	32/48
		6.25E+01	1.12E+01	1.28E+04	1.28E+04	42/50
		2.00E+02	3.57E+01	4.11E+04	4.11E+04	43/50

		6.25E+02	1.12E+02	1.28E+05	1.28E+05	69/79
	65 (NTP, 1993)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0/10
		6.25E+00	1.12E+00	1.28E+03	1.28E+03	0/10
		2.00E+01	3.57E+00	4.11E+03	4.11E+03	1/10
		6.25E+01	1.12E+01	1.28E+04	1.28E+04	9/10
		2.00E+02	3.57E+01	4.11E+04	4.11E+04	7/10
		6.25E+02	1.12E+02	1.28E+05	1.28E+05	2/2
	40 (NTP, 1993)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0/10
		6.25E+00	1.12E+00	1.28E+03	1.28E+03	0/10
		2.00E+01	3.57E+00	4.11E+03	4.11E+03	0/10
		6.25E+01	1.12E+01	1.28E+04	1.28E+04	0/10
		2.00E+02	3.57E+01	4.11E+04	4.11E+04	9/10
		6.25E+02	1.12E+02	1.28E+05	1.28E+05	8/8
	61(NTP, 1984)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	2/49
		6.25E+02	1.12E+02	1.28E+05	1.28E+05	40/45
		1.25E+03[a]	2.23E+02	2.57E+05	2.57E+05	40/48
	13 (Bevan et al., 1996)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0/10
		1.00E+03	1.79E+02	2.05E+05	2.05E+05	6/10
Rat	105 (Owen et al., 1987)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0/110
		1.00E+03	1.79E+02	1.10E+04	9.70E+02	0/110
		8.00E+03	1.43E+03	8.82E+04	7.76E+03	0/110
	13 (Bevan et al., 1996)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0/10
		1.00E+03	1.79E+02	1.10E+04	9.70E+02	0/10
	9-10 (Marty et al., 2021)	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0/12
		3.00E+02	5.36E+01	3.31E+03	2.91E+02	0/12
		1.50E+03	2.68E+02	1.65E+04	1.46E+03	0/12
		6.00E+03	1.07E+03	6.61E+04	5.82E+03	0/12

[a]Dose group dropped from dose-response data set since near maximal response reported in lower dose group.

Calculations used to calculate human equivalent concentrations used in benchmark dose modeling efforts are described below.

- *Step 1*: In Column 4 in **Table 2**, continuous exposure values were calculated by multiplying the tested concentration values (in Column 3) by a factor of 0.179 (6/24 hours per day x 5/7 days per week). [Note – the term for 5/7 days/week was inadvertently omitted from Table 2 of Kirman et al. 2022; our apologies for any confusion created by this omission].
- *Step 2*: In Column 5, human equivalent concentrations were calculated by dividing the continuous concentration values (in Column 4) by DDEF values of 0.00087 for mice or 0.0162 for rats to account for species differences in internal doses of the diepoxide metabolite, DEB, based upon the proposed MOA described above. Please see Kirman et al. (2022) for the data used to derive the DDEF values.

- *Step 3*: In Column 6, to support benchmark dose runs for mouse and rat data combined, the human equivalent concentration values calculated for rats were further adjusted to account for species differences in sensitivity to DEB (i.e., toxicodynamic differences based on Doerr et al. 1995, 1996) by multiplying the human equivalent concentrations in Column 5 by a factor of 0.088 (i.e., shifting all rat data points to the left by a factor of 11). Please see Kirman et al. (2022) for the data used to derive this adjustment factor value.
- *Step 4*: USEPA's multistage-Weibull (MSW) time-to-response model was fit to the dose-response data in Columns 6 and 7. Where possible the grouped data were further split to include individual values for exposure duration (i.e., based on day of sacrifice or found moribund as reported individual animal data appendices provided by NTP, 1993)). For mouse runs, the data in Rows 3-25 were used, and for mouse and rat combined runs, the data in Rows 3-34 were used. Data file used as input to the MSW modeling, which includes data expressed on an individual animal basis (using day of death from NTP individual animal data appendices to define individual exposures durations) are provided in **Attachment 1** for mouse and rat data combined, and for mouse data alone. Within this attachment, a duration of 83.2 weeks in rodents was defined to correspond approximately to 60 years in humans as described in Kirman and Grant (2012).

2.3 SAS Modeling of SBR Cohort Data

It is our understanding that the epidemiology data for the SBR cohort has been provided to USEPA by IISRP. The following paragraphs describe the steps that were performed to help understand the process of going from the raw SBR epidemiological data on BD exposures provided by the UAB to the models fit.

Raw SBR data provided by the University of Alabama, Birmingham (UAB)

The SAS data files received from the UAB were the following:
cv_demog_file1.sas7bdat
cv_exphist_file2_withplant.sas7bdat

The documentation for those two files is in **Table 3** and **4**, respectively.

Preprocessing of the SBR data provided by the UAB

The information in the SAS data files cv_demog_file1.sas7bdat and cv_exphist_file2_withplant.sas7bdat were processed to create the SAS file bdsas2009.sas7bdat. This file merged the information in the two original files to create a single record for each worker. **Table 5** documents the contents of the SAS merged file bdsas2009.sas7bdat.

Running the proportional hazards model in SAS

The SAS code reads the file bdsas2009.sas7bdat using the Data procedure to create other variables into a temporary SAS file. The new variables created are FUstartAge=startFUdate-birthdate and FUendAge=endFUdate-birthdate that define the starting and ending age of follow up (in days) for each individual worker. Similarly, a new variable sexN was defined as 0 for female workers and 1 for male workers. The temporary SAS file created by the Data procedure includes all the variables in the bdsas2009.sas7bdat SAS file in addition to the variables created in the Data procedure.

Using the temporary SAS file, the PHReg procedure is used to fit the proportional hazards model to the epidemiological data. The PHReg procedure uses age of the worker as the index variable so that the model is specified as:

model (FUstartAge, FUendAge)*&Response(0) = &dMetric &Covariates/ ties=exact;

where,

&Response could be any of the responses in the temporary SAS file created (e.g., Leukemia, NHL, etc.)

&dMetric could be any of the dose metrics defined in the temporary SAS file created (e.g., BDppmdays that is interpolated from the arrays defined by the age in t0 to t120 and the cumulative ppm-days in BDavg0 to BDavg120)

&Covariates could be any covariates of interest defined in the temporary SAS file created in the Data SAS procedure (e.g., sexN, Race, Plant, etc.)

The SAS code used to fit the Cox proportional hazards exposure response models to the SBR data is provided in **Attachment 2**. Please note that this appendix contains three SAS code files as used to support the publication of Valdez-Flores et al. (2022), and does not include any documentation or instructions (please reach out the BD risk assessment team if you have any questions).

Input from the science advisory panel (SAP; **Appendix B**) recommended that the assumptions of the Cox proportional hazards modeling be checked. For this reason, an evaluation of the assumptions is provided **Attachment 3**, which concludes that the final PH models presented in the BD publication do satisfy the assumptions for the time-independent covariate included in the models.

Table 3. Documentation for file cv_demog_file1.sas7bdat

File 1. **Demographic File**, UAB synthetic rubber industry 6-plant cohort, men and women combined (21,087 records*)			
Variable name	Description	Type (Char/Num)	Valid values
ID†	Identification number	N	1 - 21087
YEAR_BIRTH	Year of birth	N	1877 - 1971
SEX	Sex	C	M=Male; F=Female
RACE	Race	N	1 = white/unknown; 2 = other
LEUK_CODE	Leukemia indicator	N	0 = not leukemia 1 = lymphoid leukemia 2 = myeloid leukemia 3 = other/unknown type of leukemia
MM_CODE	Multiple myeloma indicator	N	0 = not a multiple myeloma 1 = multiple myeloma
NHL_CODE	Non-Hodgkin lymphoma indicator	N	0 = not non-Hodgkin lymphoma 1 = Non-Hodgkin lymphoma
BLADDER_CODE	Bladder/other urinary tract cancer indicator	N	0 = not non-renal urinary tract cancer 1 = bladder cancer 2 = other non-renal urinary tract cancer only (no bladder cancer)
LUNG_CODE	Lung cancer indicator	N	0 = not a lung cancer 1 = lung cancer
AGE_START	Age (decimalized years) at start of follow-up, computed as (follow-up start date – birth date)	N	13.5578 - 71.2088
AGE_END	Age (decimalized years) at end of follow-up, computed as (follow-up end date – birth date)	N	18.4038 - 109.5770
*One female subject, included in previous analyses of the 6-plant cohort, excluded due to determining that she worked at plant 2, then at plant 6. Workers ever employed at plants 2 or 5 were not eligible for inclusion in the 6-plant cohort because monomer exposure estimates were not developed for those 2 plants. †Same randomly generated ID used for File #1 as used for File #2.			

Table 4. Documentation for file cv_exphist_file2_withplant.sas7bdat

File 2. **Exposure History File**, UAB synthetic rubber industry 6-plant cohort, men and women combined (386,837 records) (sequential job records; jobs spanning >1 calendar year are split by calendar year)			
Variable name	Description	Type (N=Num)	Valid values
ID	Identification number (random number)	N	1 - 21087
PLANT	Plant code for job segment	N	1 - 8
JOB_SEQ	Sequential job segment sequence number; determined by start date of job segment	N	1 - 100
JOB_YEAR	Calendar year of job segment; each job segment can span only 1 calendar year	N	1943-1991
JOB_DUR	Duration of job in days	N	0 - 366
BD_ppm	BD 8-hr TWA (ppm) for this job	N	0 - 421.89169
BD_HITS	BD annual number of high-intensity tasks	N	0 - 4819.4297
BD_ppm_AT	BD 8-hr TWA above the threshold	N	0 - 401.87958
BD_ppm_BT	BD 8-hr TWA below the threshold	N	0 - 73.77380
STY_ppm	STY 8-hr TWA (ppm)	N	0 - 67.85346
STY_HITS	STY annual number of high-intensity tasks	N	0 - 10828.1
STY_ppm_AT	STY 8-hr TWA above the threshold	N	0 - 53.0734
STY_ppm_BT	STY 8-hr TWA below the threshold	N	0 - 26.8575

Table 5: Documentation for file bdsas2009.sas7bdat

File 3. Combined **Demographic File and Exposure History File**, UAB synthetic rubber industry 6-plant cohort, men and women combined (21,087 records)			
Variable name	Description	Type (C=Char, N=Num)	Valid values
ID	Identification number	N	1 - 21087
Study Yr	Year included in study	N	2005, 2009
Birthdate	Inferred day of birth	N	1/1/1881 – 9/9/1960
StartFUdate	Date start of follow up	N	1/1/1943 – 12/20/1991
EndFUdate	Date end of follow up	N	12/31/1943 – 12/31/2009
Sex	Sex	C	M=Male; F=Female
Race	Race	N	1 = white/unknown; 2 = other
Leukemia	Leukemia indicator	N	0 = not leukemia 1 = lymphoid leukemia 2 = myeloid leukemia 3 = other/unknown type of leukemia
Multmye	Multiple myeloma indicator	N	0 = not a multiple myeloma 1 = multiple myeloma
NHL	Non-Hodgkin lymphoma indicator	N	0 = not non-Hodgkin lymphoma 1 = Non-Hodgkin lymphoma
Bladder	Bladder/other urinary tract cancer indicator	N	0 = not non-renal urinary tract cancer 1 = bladder cancer 2 = other non-renal urinary tract cancer only (no bladder cancer)
Lung	Lung cancer indicator	N	0 = not a lung cancer 1 = lung cancer
Plant	Plant code for job segment	N	1 - 8
t0 to t120	Age (in days) at each date of exposure level change (t0 is the age of first exposure)	N	4,562 – 12,322
BDavg0 to BDavg120	Cumulative BD 8-hr TWA (ppm-days) of exposure by age t0 to t120, respectively (BDavg0 is 0 by definition)	N	>=0
BDpkAvg0 to BDpkAvg120	Cumulative BD HITs (HITs-days) of exposure by age t0 to t120, respectively (BDpkAvg0 is 0 by definition)	N	>=0

BDgtAvg0 to BDgtAvg120	Cumulative BD 8-hr TWA above the threshold (>100 ppm) of exposure by age t0 to t120, respectively (BDgtAvg0 is 0 by definition)	N	>=0
BDltAvg0 to BDltAvg120	Cumulative BD 8-hr TWA below the threshold (<100 ppm) of exposure by age t0 to t120, respectively (BDltAvg0 is 0 by definition)	N	>=0
STYavg0 to STYavg120	Cumulative STY 8-hr TWA (ppm-days) of exposure by age t0 to t120, respectively (DTYavg0 is 0 by definition)	N	>=0
STYpkAvg0 to STYpkAvg120	Cumulative STY HITs (HITs-days) of exposure by age t0 to t120, respectively (STYpkAvg0 is 0 by definition)	N	>=0
STYgtAvg0 to STYgtAvg120	Cumulative STY 8-hr TWA above the threshold (>50 ppm) of exposure by age t0 to t120, respectively (STYgtAvg0 is 0 by definition)	N	>=0
STYltAvg0 to STYltAvg120	Cumulative STY 8-hr TWA below the threshold (<50 ppm) of exposure by age t0 to t120, respectively (STYltAvg0 is 0 by definition)	N	>=0

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Attachments

Attachment 1. Input Data for Multistage-Weibull Time-to-Response Model for Ovarian Atrophy

A1.1 Mouse and Rat Data Combined (text below serves as the ".(d)" input text file for USEPA's MSW software)

```
Multistage Weibull
2
BD Ovarian Atrophy Mouse and Rat
BD_MR_Rev.set
BD_MR_Rev.out
0
0
914
-9999.0 0.0 -9999.0 -9999.0 -9999.0 -9999.0
0
8 32 32
36 1.0e-8 1.0e-8
1 0.01 0 0 83.2
1 8 0.75
1 10.000 68.8
1 4 0.95
DOSE CLASS TIME
0       C       40
0       C       40
0       C       40
0       C       40
0       C       40
0       C       40
0       C       40
0       C       40
0       C       40
0       C       40
0       C       59
0       C       65
0       C       65
0       C       65
0       C       65
0       C       65
0       C       65
0       C       65
0       C       65
0       C       65
```

0	C	70
0	C	79
0	C	80
0	C	89
0	C	90
0	C	92
0	C	94
0	C	97
0	C	100
0	C	102
0	C	106
0	C	106
0	C	106
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0	C	106
1283	C	65
1283	C	65

1283	C	65
1283	C	65
1283	C	65
1283	C	65
1283	C	65
1283	C	65
1283	C	65
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1283	C	75
1283	C	75
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1283	C	82
1283	C	92
1283	C	92
1283	C	92
1283	C	94
1283	I	97
1283	I	100
1283	C	100
1283	I	104
1283	I	105
1283	I	105
1283	I	105
1283	I	105
1283	I	105
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1283	I	105
1283	I	105
1283	I	105
1283	I	105
1283	C	105
1283	C	105
1283	C	105
1283	C	105
1283	C	105
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1283	C	105
1283	C	105
1283	C	105
1283	C	105
1283	I	106
1283	I	106
1283	I	106

1283	I	106
1283	C	106
1283	C	106
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1283	C	106
1283	C	106
1283	C	106
1283	C	106
1283	C	106
1283	C	106
1283	C	106
4105	C	28
4105	C	53
4105	I	65
4105	C	65
4105	C	65
4105	C	65
4105	C	65
4105	C	65
4105	C	65
4105	C	65
4105	C	65
4105	C	65
4105	I	71
4105	C	73
4105	C	77
4105	C	78
4105	C	78
4105	I	82
4105	C	82
4105	C	86
4105	I	87
4105	I	90
4105	I	93
4105	I	93
4105	I	94
4105	C	94
4105	C	94
4105	I	97
4105	C	97
4105	I	98
4105	I	98
4105	C	98
4105	C	99

4105	I	100
4105	I	105
4105	I	105
4105	I	105
4105	I	105
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12828	C	40
12828	C	40
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12828	C	40
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12828	I	56
12828	C	59
12828	C	60
12828	I	65
12828	I	65
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12828	I	65

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12828	I	65
12828	I	65
12828	I	65
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12828	I	76
12828	I	77
12828	I	78
12828	I	78
12828	I	82
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12828	C	93
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12828	I	100
12828	C	100
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12828	I	104
12828	C	104
12828	I	105
12828	I	105
12828	I	105
12828	I	105
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A1.2 Mouse Data Alone (text below serves as the ".(d)" input text file for USEPA's MSW software)

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1 8 0.75
1 10.000 68.8
1 4 0.95
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128284	I	50
128284	I	51
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128284	I	58
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128284	I	65
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128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	C	61
128284	C	61
128284	C	61
128284	C	61
128284	C	61
0	C	13
0	C	13
0	C	13
0	C	13
0	C	13
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0	C	13
0	C	13
0	C	13
0	C	13
205255	I	13
205255	I	13
205255	I	13

205255	I	13
205255	I	13
205255	I	13
205255	C	13
205255	C	13
205255	C	13

Attachment 2. Three SAS Code Files for CPH Modeling

A2.1 OneCovX2020PH-Shared.SAS

Note – The text below corresponds to the SAS file "OneCovX2020PH-Shared.SAS" containing the code where the options for the proportional hazards models are specified. The file currently includes the code to run the six models listed in Table 13 of Valdez-Flores et al. (2022). This file OneCovX2020PH-Shared.SAS calls the SAS file COXMODEL2020PH-shared.SAS to run the models.

```
/* Models reported in Table 13 of the BD 2021 paper

1st Argument:
"'M','F'" => Include Males & Females,  "'M'" => Include Males only, "'F'" => Include females only

2nd Argument:
lagYrs (lag) = exclude exposures that occurred within the last lagYrs

3rd Argument:
excYrs = = exclude exposures that occurred more than excYrs years ago (-1 means do not
exclude old exposures)

4th Argument:
dMetric (exposure metric; e.g. BBppmYrs for continuous BD ppm-years or
        BDppm1 BDppm2 BDppm3 BDppm4 BDppm5 BDppm6 BDppm7 BDppm8 BDppm9
BDppm10 BDppm0 for categorical (deciles) of BD ppm-years

5th Argument:
Covariates: e.g, sexN, or Plant, or BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0 for categorical BD
HITs

6th Argument:
Respones = endpoint e.g., Leukemia, or Bladder, etc.

*/

/* include previously defined macro */

%include 'C:\work\bd\2020\cox-runs - wPlant\CoxModel2020-shared.sas';
%FitPH("'M','F'", 0, -1, BDppmYrs, , Leukemia);
%FitPH("'M','F'", 0, -1, BDppmYrs, , Bladder);
%FitPH("'M','F'", 0, -1, BDppmYrs, , LeukBlad);

%FitPH("'M','F'", 0, -1, BDppmYrs, BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0, Leukemia);
```

```
%FitPH("'M','F'", 0, -1, BDppmYrs, SexN, Bladder);
%FitPH("'M','F'", 0, -1, BDppmYrs, BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0 SexN, LeukBlad);
endsas;
```

A2.2 COXMODEL2020PH-shared.SAS

Note - The text below corresponds to the SAS file "COXMODEL2020PH-shared.SAS" containing the code that actually fits the models specified in the file OneCovX2020PH-Shared.SAS

```
Options ls=90  ps=32000 NoDate; * Mprint;
*This is similar to CoxModelAllExp.sas but also does Myeloid or Lymphoid endpoints with the
grids of covariates used for Leukemia;
   /*-------------------------------------------------------
     The sas data file BDsas is used
  ------------------------------------------------------------ */

Title1 '';
Title2 '';

%Global LogL;

LibName Here 'c:\work\bd\2020\UABdata\Proc_10_28_20\';

  /*---> Specify data to use ---;*/
%macro getdata(sexin, Response);

data CoxData;
  set Here.BDsas2009;
  where sex in ("&SexIn");
  FUstartAge=startFUdate-birthdate;
  FUendAge=endFUdate-birthdate;

  RaceN = race;
  If sex = 'F' Then SexN = 0;
           else SexN = 1;

  LymphoidLeuk = 0; MyeloidLeuk = 0;
  if Leukemia = 1 then LymphoidLeuk = 1;
  if Leukemia = 2 then MyeloidLeuk = 1;

  *next two lines create a new response for leukemia or bladder/urinary cancer;

  if Leukemia > 0 or Bladder > 0 Then LeukBlad = 1;
                   else LeukBlad = 0;
run;

proc freq data=CoxData;
```

```
/*  tables Leukemia;
  tables AML;
  tables CLL;
  tables CML;
  tables Myeloid;
  tables Lymphoid; */

  tables &Response;
  tables plant;
  tables sexN;
  tables raceN;

run;

%mend getData;

*=============================================================================
====================;
%Macro FitPH(SexIn, lagYrs, excYrs, dMetric, Covariates, Response);
  Title1 "Sex = &SexIn.";
  Title2 "Endpoint = &Response.       &dMetric.-Years with Age as index variable";
  Title3 "Covariates: &Covariates.";
  Title4 "Lag = &lagYrs. and also exclude exposures that occurred &excYrs. or more years ago";

  %getdata(&SexIn, &Response);

  proc phreg data=coxData;
   model (FUstartAge, FUendAge)*&Response(0) = &dMetric &Covariates / ties=Exact;

   /* model (FUstartAge, FUendAge)*&Response(0) = &dMetric &Covariates Interact/ ties=Exact;
                              Interact=(FUendAge - FUstartAge)*SexN; */

   /* Homogeneity: Test &dMetric = 0.0003159; */  /*Tests Ho:Beta=0.0003159 using Wald's
Statistic */
   /* model (FUstartAge, FUendAge)*&Response(0) = &dMetric &Covariates/ ties=Breslow
FIRTH; */ /* can be used when not converging: See Allison p. 141 works only with
Ties=Breslow*/
   array xt{*} t0-t120;
   array cumBDPPMdays{*} BDavg0-BDavg120;
   array cumBDPKdays{*} BDpkAvg0-BDpkAvg120;
   array cumBDLTPPMdays{*} BDltAvg0-BDltAvg120;
   array cumBDGTPPMdays{*} BDgtAvg0-BDgtAvg120;
   /* array cumDMDTCdays{*} DMDTCavg0-DMDTCavg120; */
   array cumSTYPPMdays{*} STYavg0-STYavg120;
```

```
  array cumSTYPKdays{*} STYpkAvg0-STYpkAvg120;
  array cumSTYLTPPMdays{*} STYltAvg0-STYltAvg120;
  array cumSTYGTPPMdays{*} STYgtAvg0-STYgtAvg120;

  lagDays = &lagYrs*365.25;
  excDays = &excYrs*365.25;

  *The cumulative exposure is that between t-excDays and t-lagDays, if excDays < 0 then
   the cumulative exposure is that between 0 and t-lagDays.  Note: excDays > lagDays to have a
window of exposure;

  *Calculate the cumulative exposure to be excluded because occurred before excDays ago;
  BDppmdaysExcl = 0;
  BDpeakdaysExcl = 0;
  BDLTppmdaysExcl = 0;
  BDGTppmdaysExcl = 0;
  *DMDTCdaysExcl = 0;
  STYppmdaysExcl = 0;
  STYpeakdaysExcl = 0;
  STYLTppmdaysExcl = 0;
  STYGTppmdaysExcl = 0;
  if excDays > 0 then do;
    currTime = FUendAge - excDays;
    found=0;
    do i=1 to 121 until (found);
      if xt{i}>=currTime and xt{i}~=. then do;
        if i>1 then do;
          BDppmdaysExcl = cumBDPPMdays{i-1} + (currTime-xt{i-1}) *
                    (cumBDPPMdays{i}-cumBDPPMdays{i-1}) / (xt{i}-xt{i-1});
          BDpeakdaysExcl = cumBDPKdays{i-1} + (currTime-xt{i-1}) *
                    (cumBDPKdays{i}-cumBDPKdays{i-1}) / (xt{i}-xt{i-1});
          BDLTppmdaysExcl = cumBDLTPPMdays{i-1} + (currTime-xt{i-1}) *
                    (cumBDLTPPMdays{i}-cumBDLTPPMdays{i-1}) / (xt{i}-xt{i-1});
          BDGTppmdaysExcl = cumBDGTPPMdays{i-1} + (currTime-xt{i-1}) *
                    (cumBDGTPPMdays{i}-cumBDGTPPMdays{i-1}) / (xt{i}-xt{i-1});
          *DMDTCdaysExcl = cumDMDTCdays{i-1} + (currTime-xt{i-1}) *
                    (cumDMDTCdays{i}-cumDMDTCdays{i-1}) / (xt{i}-xt{i-1});
          STYppmdaysExcl = cumSTYPPMdays{i-1} + (currTime-xt{i-1}) *
                    (cumSTYPPMdays{i}-cumSTYPPMdays{i-1}) / (xt{i}-xt{i-1});
          STYpeakdaysExcl = cumSTYPKdays{i-1} + (currTime-xt{i-1}) *
                    (cumSTYPKdays{i}-cumSTYPKdays{i-1}) / (xt{i}-xt{i-1});
          STYLTppmdaysExcl = cumSTYLTPPMdays{i-1} + (currTime-xt{i-1}) *
                    (cumSTYLTPPMdays{i}-cumSTYLTPPMdays{i-1}) / (xt{i}-xt{i-1});
          STYGTppmdaysExcl = cumSTYGTPPMdays{i-1} + (currTime-xt{i-1}) *
```

```
                    (cumSTYGTPPMdays{i}-cumSTYGTPPMdays{i-1}) / (xt{i}-xt{i-1});
      end;
      *if i=1 then stop;
      *before xt{1} exposure is zero and worker was not at risk and this should not occur;

      found=1;
    end;
    else if xt{i}=. & i>1 then do;
      BDppmdaysExcl = cumBDPPMdays{i-1};
      BDpeakdaysExcl = cumBDPKdays{i-1};
      BDLTppmdaysExcl = cumBDLTPPMdays{i-1};
      BDGTppmdaysExcl = cumBDGTPPMdays{i-1};
      *DMDTCdaysExcl = cumDMDTCdays{i-1};
      STYppmdaysExcl = cumSTYPPMdays{i-1};
      STYpeakdaysExcl = cumSTYPKdays{i-1};
      STYLTppmdaysExcl = cumSTYLTPPMdays{i-1};
      STYGTppmdaysExcl = cumSTYGTPPMdays{i-1};
      found=1;
    end;
  end;
end;

*Calculate the cumulative exposure to be excluded because up to t-lagDays;
  currTime = FUendAge - lagDays;
  found=0;
  do i=1 to 121 until (found);
    if xt{i}>=currTime and xt{i}~=. then do;
      if i=1 then do;
        BDppmdays = 0;
        BDpeakdays = 0;
        BDLTppmdays = 0;
        BDGTppmdays = 0;
        *DMDTCdays = 0;
        STYppmdays = 0;
        STYpeakdays = 0;
        STYLTppmdays = 0;
        STYGTppmdays = 0;
      end;
      else do;
        BDppmdays = cumBDPPMdays{i-1} + (currTime-xt{i-1}) *
                    (cumBDPPMdays{i}-cumBDPPMdays{i-1}) / (xt{i}-xt{i-1});
        BDpeakdays = cumBDPKdays{i-1} + (currTime-xt{i-1}) *
                    (cumBDPKdays{i}-cumBDPKdays{i-1}) / (xt{i}-xt{i-1});
        BDLTppmdays = cumBDLTPPMdays{i-1} + (currTime-xt{i-1}) *
```

```
                (cumBDLTPPMdays{i}-cumBDLTPPMdays{i-1}) / (xt{i}-xt{i-1});
      BDGTppmdays = cumBDGTPPMdays{i-1} + (currTime-xt{i-1}) *
                (cumBDGTPPMdays{i}-cumBDGTPPMdays{i-1}) / (xt{i}-xt{i-1});
      *DMDTCdays = cumDMDTCdays{i-1} + (currTime-xt{i-1}) *
                (cumDMDTCdays{i}-cumDMDTCdays{i-1}) / (xt{i}-xt{i-1});
      STYppmdays = cumSTYPPMdays{i-1} + (currTime-xt{i-1}) *
                (cumSTYPPMdays{i}-cumSTYPPMdays{i-1}) / (xt{i}-xt{i-1});
      STYpeakdays = cumSTYPKdays{i-1} + (currTime-xt{i-1}) *
                (cumSTYPKdays{i}-cumSTYPKdays{i-1}) / (xt{i}-xt{i-1});
      STYLTppmdays = cumSTYLTPPMdays{i-1} + (currTime-xt{i-1}) *
                (cumSTYLTPPMdays{i}-cumSTYLTPPMdays{i-1}) / (xt{i}-xt{i-1});
      STYGTppmdays = cumSTYGTPPMdays{i-1} + (currTime-xt{i-1}) *
                (cumSTYGTPPMdays{i}-cumSTYGTPPMdays{i-1}) / (xt{i}-xt{i-1});
    end;
    *if i=1 then stop;
    *before xt{1} exposure is zero and worker was not at risk and this should not occur;

    found=1;
  end;
  else if xt{i}=. & i>1 then do;
    BDppmdays = cumBDPPMdays{i-1};
    BDpeakdays = cumBDPKdays{i-1};
    BDLTppmdays = cumBDLTPPMdays{i-1};
    BDGTppmdays = cumBDGTPPMdays{i-1};
    *DMDTCdays = cumDMDTCdays{i-1};
    STYppmdays = cumSTYPPMdays{i-1};
    STYpeakdays = cumSTYPKdays{i-1};
    STYLTppmdays = cumSTYLTPPMdays{i-1};
    STYGTppmdays = cumSTYGTPPMdays{i-1};
    found=1;
  end;
end;


BDppmYrs = (BDppmdays - BDppmdaysExcl) / 365.25;
BDpeakYrs = (BDpeakdays - BDpeakdaysExcl) / 365.25;
BDLTppmYrs = (BDLTppmdays - BDLTppmdaysExcl) / 365.25;
BDGTppmYrs = (BDGTppmdays - BDGTppmdaysExcl) / 365.25;
* DMDTCYrs = (DMDTCdays - DMDTCdaysExcl) / 365.25;

      STYppmYrs = (STYppmdays - STYppmdaysExcl) / 365.25;
STYpeakYrs = (STYpeakdays - STYpeakdaysExcl) / 365.25;
STYLTppmYrs = (STYLTppmdays - STYLTppmdaysExcl) / 365.25;
STYGTppmYrs = (STYGTppmdays - STYGTppmdaysExcl) / 365.25;
```

```
        BDppm0 = 0; BDppm1 = 0; BDppm2 = 0; BDppm3 = 0; BDppm4 = 0; BDppm5 = 0;
BDppm6 = 0; BDppm7 = 0; BDppm8 = 0; BDppm9 = 0; BDppm10 = 0;
    BDpk0 = 0; BDpk1 = 0; BDpk2 = 0; BDpk3 = 0; BDpk4 = 0; BDpk5 = 0;
    BDlt0 = 0; BDlt1 = 0; BDlt2 = 0; BDlt3 = 0; BDlt4 = 0; BDlt5 = 0;
    BDgt0 = 0; BDgt1 = 0; BDgt2 = 0; BDgt3 = 0; BDgt4 = 0; BDgt5 = 0;

    /* DMDTC0 = 0; DMDTC1 = 0; DMDTC2 = 0; DMDTC3 = 0; DMDTC4 = 0; DMDTC5 = 0; */
    STY0 = 0; STY1 = 0; STY2 = 0; STY3 = 0; STY4 = 0; STY5 = 0;
    STYpk0 = 0; STYpk1 = 0; STYpk2 = 0; STYpk3 = 0; STYpk4 = 0; STYpk5 = 0;
    STYlt0 = 0; STYlt1 = 0; STYlt2 = 0; STYlt3 = 0; STYlt4 = 0; STYlt5 = 0;
    STYgt0 = 0; STYgt1 = 0; STYgt2 = 0; STYgt3 = 0; STYgt4 = 0; STYgt5 = 0;

    YSH0 = 0; YSH1 = 0; YSH2 = 0; YSH3 = 0; YSH4 = 0;
    CalYr0 = 0; CalYr1 = 0; CalYr2 = 0; CalYr3 = 0; CalYr4 = 0;

    DaysSH = (FUendAge - xt{1});
    YSH=DaysSH/365.25;
    CalYrSince01011960 = (BirthDate + xt{1} + DaysSH)/365.25;
    CalYr = 1960 + CalYrSince01011960;

     if "&Response" = 'Leukemia' or "&Response" = 'LeukBlad' then do;

       if BDppmYrs = 0 then BDppmYrsDec=0;
         else if BDppmYrs <=  12.286776  then BDppmYrsDec = 7.64909545454545;
         else if BDppmYrs <=  25.44995  then BDppmYrsDec = 18.394273;
         else if BDppmYrs <=  42.376384  then BDppmYrsDec = 34.561552;
         else if BDppmYrs <=  64.271944  then BDppmYrsDec = 51.806062;
         else if BDppmYrs <=  121.2756  then BDppmYrsDec = 83.2182509090909;
         else if BDppmYrs <=  207.5064  then BDppmYrsDec = 172.88178;
         else if BDppmYrs <=  281.1159  then BDppmYrsDec = 242.56641;
         else if BDppmYrs <=  435.08458  then BDppmYrsDec = 348.37726;
         else if BDppmYrs <=  814.922320000002  then BDppmYrsDec = 590.61346;
         else BDppmYrsDec = 2018.68676363636;

       if BDppmYrs = 0 then BDppm0=1;
         else if BDppmYrs <=  12.286776  then BDppm1 = 1;
         else if BDppmYrs <=  25.44995  then BDppm2 = 1;
         else if BDppmYrs <=  42.376384  then BDppm3 = 1;
         else if BDppmYrs <=  64.271944  then BDppm4 = 1;
         else if BDppmYrs <=  121.2756  then BDppm5 = 1;
         else if BDppmYrs <=  207.5064  then BDppm6 = 1;
         else if BDppmYrs <=  281.1159  then BDppm7 = 1;
         else if BDppmYrs <=  435.08458  then BDppm8 = 1;
```

```
  else if BDppmYrs <=  814.922320000002  then BDppm9 = 1;
  else BDppm10 = 1;

if BDpeakYrs = 0 then BDpk0 = 1;
  else if BDpeakYrs <=  241.98704  then BDpk1 = 1;
  else if BDpeakYrs <=  499.18794  then BDpk2 = 1;
  else if BDpeakYrs <=  1812.4162  then BDpk3 = 1;
  else if BDpeakYrs <=  3307.4268  then BDpk4 = 1;
  else BDpk5 = 1;

if BDGTppmYrs = 0 then BDgt0 = 1;
  else if BDGTppmYrs <=  13.814716  then BDgt1 = 1;
  else if BDGTppmYrs <=  35.45475  then BDgt2 = 1;
  else if BDGTppmYrs <=  107.33322  then BDgt3 = 1;
  else if BDGTppmYrs <=  248.77784  then BDgt4 = 1;
  else BDgt5 = 1;

if BDLTppmYrs = 0 then BDlt0 = 1;
  else if BDLTppmYrs <=  6.5509242  then BDlt1 = 1;
  else if BDLTppmYrs <=  18.816296  then BDlt2 = 1;
  else if BDLTppmYrs <=  63.26338  then BDlt3 = 1;
  else if BDLTppmYrs <=  149.24674  then BDlt4 = 1;
  else BDlt5 = 1;

if STYppmYrs = 0 then STY0 = 1;
  else if STYppmYrs <=  4.8925118  then STY1 = 1;
  else if STYppmYrs <=  15.628216  then STY2 = 1;
  else if STYppmYrs <=  37.490402  then STY3 = 1;
  else if STYppmYrs <=  67.342098  then STY4 = 1;
  else STY5 = 1;

if STYpeakYrs = 0 then STYpk0 = 1;
  else if STYpeakYrs <=  35.423166  then STYpk1 = 1;
  else if STYpeakYrs <=  106.08006  then STYpk2 = 1;
  else if STYpeakYrs <=  215.9117  then STYpk3 = 1;
  else if STYpeakYrs <=  785.33222  then STYpk4 = 1;
  else STYpk5 = 1;

if STYGTppmYrs = 0 then STYgt0 = 1;
  else if STYGTppmYrs <=  0.085579176  then STYgt1 = 1;
  else if STYGTppmYrs <=  0.4104186  then STYgt2 = 1;
  else if STYGTppmYrs <=  1.717241  then STYgt3 = 1;
  else if STYGTppmYrs <=  14.69047  then STYgt4 = 1;
  else STYgt5 = 1;
```

```
  if STYLTppmYrs = 0 then STYlt0 = 1;
    else if STYLTppmYrs <=  3.7506464  then STYlt1 = 1;
    else if STYLTppmYrs <=  12.216846  then STYlt2 = 1;
    else if STYLTppmYrs <=  30.880882  then STYlt3 = 1;
    else if STYLTppmYrs <=  51.863964  then STYlt4 = 1;
    else STYlt5 = 1;

  if YSH <=  24.3126625598905  then YSH0 = 1;
    else if YSH <=  32.22340862423  then YSH1 = 1;
    else if YSH <=  41.0075290896646  then YSH2 = 1;
    else if YSH <=  50.5100616016427  then YSH3 = 1;
    else YSH4 = 1;

  if CalYr <=  1978  then CalYr0 = 1;
    else if CalYr <=  1990  then CalYr1 = 1;
    else if CalYr <=  1996  then CalYr2 = 1;
    else if CalYr <=  2003  then CalYr3 = 1;
    else CalYr4 = 1;

end;

else if "&Response" = 'LymphoidLeuk' then do;

  if BDppmYrs = 0 then BDppmYrsDec=0;
    else if BDppmYrs <=  11.772682  then BDppmYrsDec = 6.5178415;
    else if BDppmYrs <=  34.147382  then BDppmYrsDec = 23.90778;
    else if BDppmYrs <=  65.72234  then BDppmYrsDec = 47.70646;
    else if BDppmYrs <=  134.56626  then BDppmYrsDec = 93.6310675;
    else if BDppmYrs <=  225.4502  then BDppmYrsDec = 205.840775;
    else if BDppmYrs <=  289.86896  then BDppmYrsDec = 264.225433333333;
    else if BDppmYrs <=  370.09014  then BDppmYrsDec = 316.98765;
    else if BDppmYrs <=  466.9105  then BDppmYrsDec = 406.02785;
    else if BDppmYrs <=  944.665400000002  then BDppmYrsDec = 708.16015;
    else BDppmYrsDec = 3277.62375;

  if BDppmYrs = 0 then BDppm0=1;
    else if BDppmYrs <=  11.772682  then BDppm1 = 1;
    else if BDppmYrs <=  34.147382  then BDppm2 = 1;
    else if BDppmYrs <=  65.72234  then BDppm3 = 1;
    else if BDppmYrs <=  134.56626  then BDppm4 = 1;
    else if BDppmYrs <=  225.4502  then BDppm5 = 1;
    else if BDppmYrs <=  289.86896  then BDppm6 = 1;
    else if BDppmYrs <=  370.09014  then BDppm7 = 1;
```

```
  else if BDppmYrs <=  466.9105  then BDppm8 = 1;
  else if BDppmYrs <=  944.665400000002  then BDppm9 = 1;
  else BDppm10 = 1;

if BDpeakYrs = 0 then BDpk0 = 1;
  else if BDpeakYrs <=  242.25608  then BDpk1 = 1;
  else if BDpeakYrs <=  767.92452  then BDpk2 = 1;
  else if BDpeakYrs <=  2429.4282  then BDpk3 = 1;
  else if BDpeakYrs <=  3358.906  then BDpk4 = 1;
  else BDpk5 = 1;

if BDGTppmYrs = 0 then BDgt0 = 1;
  else if BDGTppmYrs <=  17.391288  then BDgt1 = 1;
  else if BDGTppmYrs <=  46.506264  then BDgt2 = 1;
  else if BDGTppmYrs <=  159.97986  then BDgt3 = 1;
  else if BDGTppmYrs <=  298.14908  then BDgt4 = 1;
  else BDgt5 = 1;

if BDLTppmYrs = 0 then BDlt0 = 1;
  else if BDLTppmYrs <=  9.89434280000001  then BDlt1 = 1;
  else if BDLTppmYrs <=  50.057512  then BDlt2 = 1;
  else if BDLTppmYrs <=  83.149574  then BDlt3 = 1;
  else if BDLTppmYrs <=  230.96884  then BDlt4 = 1;
  else BDlt5 = 1;

if STYppmYrs = 0 then STY0 = 1;
  else if STYppmYrs <=  6.315333  then STY1 = 1;
  else if STYppmYrs <=  14.783734  then STY2 = 1;
  else if STYppmYrs <=  40.018784  then STY3 = 1;
  else if STYppmYrs <=  76.540908  then STY4 = 1;
  else STY5 = 1;

if STYpeakYrs = 0 then STYpk0 = 1;
  else if STYpeakYrs <=  12.59083  then STYpk1 = 1;
  else if STYpeakYrs <=  76.55929  then STYpk2 = 1;
  else if STYpeakYrs <=  120.5994  then STYpk3 = 1;
  else if STYpeakYrs <=  502.323700000001  then STYpk4 = 1;
  else STYpk5 = 1;

if STYGTppmYrs = 0 then STYgt0 = 1;
  else if STYGTppmYrs <=  0.06671398  then STYgt1 = 1;
  else if STYGTppmYrs <=  0.2048831  then STYgt2 = 1;
  else if STYGTppmYrs <=  0.5367334  then STYgt3 = 1;
  else if STYGTppmYrs <=  5.43630900000006  then STYgt4 = 1;
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   else STYgt5 = 1;

  if STYLTppmYrs = 0 then STYlt0 = 1;
   else if STYLTppmYrs <=  4.8438708  then STYlt1 = 1;
   else if STYLTppmYrs <=  13.767854  then STYlt2 = 1;
   else if STYLTppmYrs <=  38.271106  then STYlt3 = 1;
   else if STYLTppmYrs <=  57.121984  then STYlt4 = 1;
   else STYlt5 = 1;

  if YSH <=  26.6639288158796  then YSH0 = 1;
   else if YSH <=  34.1744010951403  then YSH1 = 1;
   else if YSH <=  41.7248459958932  then YSH2 = 1;
   else if YSH <=  53.6678986995209  then YSH3 = 1;
   else YSH4 = 1;

  if CalYr <=  1981  then CalYr0 = 1;
   else if CalYr <=  1990  then CalYr1 = 1;
   else if CalYr <=  1998  then CalYr2 = 1;
   else if CalYr <=  2001  then CalYr3 = 1;
   else CalYr4 = 1;

end;

else if "&Response" = 'MyeloidLeuk' then do;

  if BDppmYrs = 0 then BDppmYrsDec=0;
   else if BDppmYrs <=  15.01213  then BDppmYrsDec = 10.1845101666667;
   else if BDppmYrs <=  21.152936  then BDppmYrsDec = 18.174368;
   else if BDppmYrs <=  35.920822  then BDppmYrsDec = 28.073432;
   else if BDppmYrs <=  47.072834  then BDppmYrsDec = 41.247588;
   else if BDppmYrs <=  70.05312  then BDppmYrsDec = 58.6728316666667;
   else if BDppmYrs <=  126.95416  then BDppmYrsDec = 88.865108;
   else if BDppmYrs <=  195.61318  then BDppmYrsDec = 177.08576;
   else if BDppmYrs <=  269.29806  then BDppmYrsDec = 230.15048;
   else if BDppmYrs <=  500.340240000001  then BDppmYrsDec = 382.90206;
   else BDppmYrsDec = 1231.87121666667;

  if BDppmYrs = 0 then BDppm0=1;
   else if BDppmYrs <=  15.01213  then BDppm1 = 1;
   else if BDppmYrs <=  21.152936  then BDppm2 = 1;
   else if BDppmYrs <=  35.920822  then BDppm3 = 1;
   else if BDppmYrs <=  47.072834  then BDppm4 = 1;
   else if BDppmYrs <=  70.05312  then BDppm5 = 1;
   else if BDppmYrs <=  126.95416  then BDppm6 = 1;
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  else if BDppmYrs <=  195.61318  then BDppm7 = 1;
  else if BDppmYrs <=  269.29806  then BDppm8 = 1;
  else if BDppmYrs <=  500.340240000001  then BDppm9 = 1;
  else BDppm10 = 1;

if BDpeakYrs = 0 then BDpk0 = 1;
  else if BDpeakYrs <=  247.14374  then BDpk1 = 1;
  else if BDpeakYrs <=  416.39262  then BDpk2 = 1;
  else if BDpeakYrs <=  1189.4552  then BDpk3 = 1;
  else if BDpeakYrs <=  3131.037  then BDpk4 = 1;
  else BDpk5 = 1;

if BDGTppmYrs = 0 then BDgt0 = 1;
  else if BDGTppmYrs <=  13.814716  then BDgt1 = 1;
  else if BDGTppmYrs <=  31.385464  then BDgt2 = 1;
  else if BDGTppmYrs <=  60.9162200000001  then BDgt3 = 1;
  else if BDGTppmYrs <=  177.53222  then BDgt4 = 1;
  else BDgt5 = 1;

if BDLTppmYrs = 0 then BDlt0 = 1;
  else if BDLTppmYrs <=  4.1715206  then BDlt1 = 1;
  else if BDLTppmYrs <=  15.591554  then BDlt2 = 1;
  else if BDLTppmYrs <=  40.620774  then BDlt3 = 1;
  else if BDLTppmYrs <=  98.611182  then BDlt4 = 1;
  else BDlt5 = 1;

if STYppmYrs = 0 then STY0 = 1;
  else if STYppmYrs <=  4.709336  then STY1 = 1;
  else if STYppmYrs <=  15.53368  then STY2 = 1;
  else if STYppmYrs <=  32.60183  then STY3 = 1;
  else if STYppmYrs <=  53.53916  then STY4 = 1;
  else STY5 = 1;

if STYpeakYrs = 0 then STYpk0 = 1;
  else if STYpeakYrs <=  41.700912  then STYpk1 = 1;
  else if STYpeakYrs <=  117.94  then STYpk2 = 1;
  else if STYpeakYrs <=  226.14202  then STYpk3 = 1;
  else if STYpeakYrs <=  875.945380000001  then STYpk4 = 1;
  else STYpk5 = 1;

if STYGTppmYrs = 0 then STYgt0 = 1;
  else if STYGTppmYrs <=  0.08168485  then STYgt1 = 1;
  else if STYGTppmYrs <=  0.48322594  then STYgt2 = 1;
  else if STYGTppmYrs <=  3.3537652  then STYgt3 = 1;
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   else if STYGTppmYrs <=  15.00554  then STYgt4 = 1;
   else STYgt5 = 1;

  if STYLTppmYrs = 0 then STYlt0 = 1;
   else if STYLTppmYrs <=  3.694579  then STYlt1 = 1;
   else if STYLTppmYrs <=  10.97783  then STYlt2 = 1;
   else if STYLTppmYrs <=  21.00106  then STYlt3 = 1;
   else if STYLTppmYrs <=  49.09693  then STYlt4 = 1;
   else STYlt5 = 1;

  if YSH <=  22.2981519507187  then YSH0 = 1;
   else if YSH <=  28.699794661191  then YSH1 = 1;
   else if YSH <=  36.4320328542094  then YSH2 = 1;
   else if YSH <=  48.2759753593429  then YSH3 = 1;
   else YSH4 = 1;

  if CalYr <=  1976  then CalYr0 = 1;
   else if CalYr <=  1988  then CalYr1 = 1;
   else if CalYr <=  1994  then CalYr2 = 1;
   else if CalYr <=  2002  then CalYr3 = 1;
   else CalYr4 = 1;

end;

else if "&Response" = 'MultMye' then do;

  if BDppmYrs = 0 then BDppmYrsDec=0;
   else if BDppmYrs <=  4.0451419  then BDppmYrsDec = 2.03613639125;
   else if BDppmYrs <=  25.273884  then BDppmYrsDec = 13.4698115;
   else if BDppmYrs <=  46.687032  then BDppmYrsDec = 34.682685;
   else if BDppmYrs <=  75.207558  then BDppmYrsDec = 58.659965;
   else if BDppmYrs <=  110.9812  then BDppmYrsDec = 96.3974425;
   else if BDppmYrs <=  153.24974  then BDppmYrsDec = 128.0067;
   else if BDppmYrs <=  367.53402  then BDppmYrsDec = 246.320775;
   else if BDppmYrs <=  453.29092  then BDppmYrsDec = 399.95125;
   else if BDppmYrs <=  661.93948  then BDppmYrsDec = 593.02935;
   else BDppmYrsDec = 1572.284775;

  if BDppmYrs = 0 then BDppm0=1;
   else if BDppmYrs <=  4.0451419  then BDppm1 = 1;
   else if BDppmYrs <=  25.273884  then BDppm2 = 1;
   else if BDppmYrs <=  46.687032  then BDppm3 = 1;
   else if BDppmYrs <=  75.207558  then BDppm4 = 1;
   else if BDppmYrs <=  110.9812  then BDppm5 = 1;
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  else if BDppmYrs <=  153.24974  then BDppm6 = 1;
  else if BDppmYrs <=  367.53402  then BDppm7 = 1;
  else if BDppmYrs <=  453.29092  then BDppm8 = 1;
  else if BDppmYrs <=  661.93948  then BDppm9 = 1;
  else BDppm10 = 1;

if BDpeakYrs = 0 then BDpk0 = 1;
  else if BDpeakYrs <=  184.4059  then BDpk1 = 1;
  else if BDpeakYrs <=  441.4002  then BDpk2 = 1;
  else if BDpeakYrs <=  786.1249  then BDpk3 = 1;
  else if BDpeakYrs <=  1934.201  then BDpk4 = 1;
  else BDpk5 = 1;

if BDGTppmYrs = 0 then BDgt0 = 1;
  else if BDGTppmYrs <=  18.93902  then BDgt1 = 1;
  else if BDGTppmYrs <=  42.31457  then BDgt2 = 1;
  else if BDGTppmYrs <=  148.0654  then BDgt3 = 1;
  else if BDGTppmYrs <=  413.108  then BDgt4 = 1;
  else BDgt5 = 1;

if BDLTppmYrs = 0 then BDlt0 = 1;
  else if BDLTppmYrs <=  5.147871  then BDlt1 = 1;
  else if BDLTppmYrs <=  30.99393  then BDlt2 = 1;
  else if BDLTppmYrs <=  59.841646  then BDlt3 = 1;
  else if BDLTppmYrs <=  125.34422  then BDlt4 = 1;
  else BDlt5 = 1;

if STYppmYrs = 0 then STY0 = 1;
  else if STYppmYrs <=  2.3329538  then STY1 = 1;
  else if STYppmYrs <=  9.74148459999999  then STY2 = 1;
  else if STYppmYrs <=  30.969444  then STY3 = 1;
  else if STYppmYrs <=  111.96418  then STY4 = 1;
  else STY5 = 1;

if STYpeakYrs = 0 then STYpk0 = 1;
  else if STYpeakYrs <=  28.928  then STYpk1 = 1;
  else if STYpeakYrs <=  43.13926  then STYpk2 = 1;
  else if STYpeakYrs <=  159.6191  then STYpk3 = 1;
  else if STYpeakYrs <=  374.23442  then STYpk4 = 1;
  else STYpk5 = 1;

if STYGTppmYrs = 0 then STYgt0 = 1;
  else if STYGTppmYrs <=  0.029117502  then STYgt1 = 1;
  else if STYGTppmYrs <=  0.23400414  then STYgt2 = 1;
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  else if STYGTppmYrs <=  4.9383296  then STYgt3 = 1;
  else if STYGTppmYrs <=  58.6571080000001  then STYgt4 = 1;
  else STYgt5 = 1;

 if STYLTppmYrs = 0 then STYlt0 = 1;
  else if STYLTppmYrs <=  1.8583748  then STYlt1 = 1;
  else if STYLTppmYrs <=  6.3484938  then STYlt2 = 1;
  else if STYLTppmYrs <=  24.717552  then STYlt3 = 1;
  else if STYLTppmYrs <=  60.5471020000001  then STYlt4 = 1;
  else STYlt5 = 1;

 if YSH <=  28.3734428473649  then YSH0 = 1;
  else if YSH <=  37.9559206023272  then YSH1 = 1;
  else if YSH <=  43.311704312115  then YSH2 = 1;
  else if YSH <=  48.9834360027379  then YSH3 = 1;
  else YSH4 = 1;

 if CalYr <=  1983  then CalYr0 = 1;
  else if CalYr <=  1989  then CalYr1 = 1;
  else if CalYr <=  1999  then CalYr2 = 1;
  else if CalYr <=  2003  then CalYr3 = 1;
  else CalYr4 = 1;

end;

else if "&Response" = 'NHL' then do;

 if BDppmYrs = 0 then BDppmYrsDec=0;
  else if BDppmYrs <=  4.7878375  then BDppmYrsDec = 1.75132758325;
  else if BDppmYrs <=  11.22415  then BDppmYrsDec = 8.897823;
  else if BDppmYrs <=  25.959705  then BDppmYrsDec = 19.0953471428571;
  else if BDppmYrs <=  56.61876  then BDppmYrsDec = 44.29703;
  else if BDppmYrs <=  120.8032  then BDppmYrsDec = 83.09217;
  else if BDppmYrs <=  173.8207  then BDppmYrsDec = 151.9881125;
  else if BDppmYrs <=  308.71285  then BDppmYrsDec = 258.940328571429;
  else if BDppmYrs <=  371.0099  then BDppmYrsDec = 339.3068625;
  else if BDppmYrs <=  591.073650000001  then BDppmYrsDec = 458.427585714286;
  else BDppmYrsDec = 961.8362;

 if BDppmYrs = 0 then BDppm0=1;
  else if BDppmYrs <=  4.7878375  then BDppm1 = 1;
  else if BDppmYrs <=  11.22415  then BDppm2 = 1;
  else if BDppmYrs <=  25.959705  then BDppm3 = 1;
  else if BDppmYrs <=  56.61876  then BDppm4 = 1;
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  else if BDppmYrs <=  120.8032  then BDppm5 = 1;
  else if BDppmYrs <=  173.8207  then BDppm6 = 1;
  else if BDppmYrs <=  308.71285  then BDppm7 = 1;
  else if BDppmYrs <=  371.0099  then BDppm8 = 1;
  else if BDppmYrs <=  591.073650000001  then BDppm9 = 1;
  else BDppm10 = 1;

if BDpeakYrs = 0 then BDpk0 = 1;
  else if BDpeakYrs <=  106.229  then BDpk1 = 1;
  else if BDpeakYrs <=  344.5946  then BDpk2 = 1;
  else if BDpeakYrs <=  1321.694  then BDpk3 = 1;
  else if BDpeakYrs <=  2858.062  then BDpk4 = 1;
  else BDpk5 = 1;

if BDGTppmYrs = 0 then BDgt0 = 1;
  else if BDGTppmYrs <=  3.391538  then BDgt1 = 1;
  else if BDGTppmYrs <=  37.35791  then BDgt2 = 1;
  else if BDGTppmYrs <=  122.6169  then BDgt3 = 1;
  else if BDGTppmYrs <=  240.5328  then BDgt4 = 1;
  else BDgt5 = 1;

if BDLTppmYrs = 0 then BDlt0 = 1;
  else if BDLTppmYrs <=  5.681648  then BDlt1 = 1;
  else if BDLTppmYrs <=  19.2389  then BDlt2 = 1;
  else if BDLTppmYrs <=  56.80923  then BDlt3 = 1;
  else if BDLTppmYrs <=  138.1042  then BDlt4 = 1;
  else BDlt5 = 1;

if STYppmYrs = 0 then STY0 = 1;
  else if STYppmYrs <=  4.306893  then STY1 = 1;
  else if STYppmYrs <=  13.4291  then STY2 = 1;
  else if STYppmYrs <=  32.52565  then STY3 = 1;
  else if STYppmYrs <=  72.5092300000001  then STY4 = 1;
  else STY5 = 1;

if STYpeakYrs = 0 then STYpk0 = 1;
  else if STYpeakYrs <=  20.09391  then STYpk1 = 1;
  else if STYpeakYrs <=  48.907368  then STYpk2 = 1;
  else if STYpeakYrs <=  107.28378  then STYpk3 = 1;
  else if STYpeakYrs <=  1111.9972  then STYpk4 = 1;
  else STYpk5 = 1;

if STYGTppmYrs = 0 then STYgt0 = 1;
  else if STYGTppmYrs <=  0.080989688  then STYgt1 = 1;
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   else if STYGTppmYrs <=  0.53657812  then STYgt2 = 1;
   else if STYGTppmYrs <=  3.9560878  then STYgt3 = 1;
   else if STYGTppmYrs <=  18.772016  then STYgt4 = 1;
   else STYgt5 = 1;

  if STYLTppmYrs = 0 then STYlt0 = 1;
   else if STYLTppmYrs <=  2.88448  then STYlt1 = 1;
   else if STYLTppmYrs <=  9.822338  then STYlt2 = 1;
   else if STYLTppmYrs <=  28.7915  then STYlt3 = 1;
   else if STYLTppmYrs <=  57.34761  then STYlt4 = 1;
   else STYlt5 = 1;

  if YSH <=  26.9716632443532  then YSH0 = 1;
   else if YSH <=  35.1841204654346  then YSH1 = 1;
   else if YSH <=  42.1815195071869  then YSH2 = 1;
   else if YSH <=  49.4318959616701  then YSH3 = 1;
   else YSH4 = 1;

  if CalYr <=  1982  then CalYr0 = 1;
   else if CalYr <=  1991  then CalYr1 = 1;
   else if CalYr <=  1998  then CalYr2 = 1;
   else if CalYr <=  2004  then CalYr3 = 1;
   else CalYr4 = 1;

end;

else if "&Response" = 'Bladder' then do;

  if BDppmYrs = 0 then BDppmYrsDec=0;
   else if BDppmYrs <=  10.912895  then BDppmYrsDec = 5.9113829875;
   else if BDppmYrs <=  29.40545  then BDppmYrsDec = 19.4562875;
   else if BDppmYrs <=  43.22105  then BDppmYrsDec = 36.3178585714286;
   else if BDppmYrs <=  52.23105  then BDppmYrsDec = 47.446875;
   else if BDppmYrs <=  90.799045  then BDppmYrsDec = 70.5432771428572;
   else if BDppmYrs <=  152.5102  then BDppmYrsDec = 129.60044;
   else if BDppmYrs <=  239.6775  then BDppmYrsDec = 189.412628571429;
   else if BDppmYrs <=  506.921900000001  then BDppmYrsDec = 388.3455;
   else if BDppmYrs <=  870.686850000002  then BDppmYrsDec = 686.887685714286;
   else BDppmYrsDec = 2963.072175;

  if BDppmYrs = 0 then BDppm0=1;
   else if BDppmYrs <=  10.912895  then BDppm1 = 1;
   else if BDppmYrs <=  29.40545  then BDppm2 = 1;
   else if BDppmYrs <=  43.22105  then BDppm3 = 1;
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  else if BDppmYrs <=  52.23105  then BDppm4 = 1;
  else if BDppmYrs <=  90.799045  then BDppm5 = 1;
  else if BDppmYrs <=  152.5102  then BDppm6 = 1;
  else if BDppmYrs <=  239.6775  then BDppm7 = 1;
  else if BDppmYrs <=  506.921900000001  then BDppm8 = 1;
  else if BDppmYrs <=  870.686850000002  then BDppm9 = 1;
  else BDppm10 = 1;

if BDpeakYrs = 0 then BDpk0 = 1;
  else if BDpeakYrs <=  245.27572  then BDpk1 = 1;
  else if BDpeakYrs <=  569.9204  then BDpk2 = 1;
  else if BDpeakYrs <=  1869.2506  then BDpk3 = 1;
  else if BDpeakYrs <=  3732.1662  then BDpk4 = 1;
  else BDpk5 = 1;

if BDGTppmYrs = 0 then BDgt0 = 1;
  else if BDGTppmYrs <=  12.798482  then BDgt1 = 1;
  else if BDGTppmYrs <=  33.530716  then BDgt2 = 1;
  else if BDGTppmYrs <=  122.12312  then BDgt3 = 1;
  else if BDGTppmYrs <=  342.05056  then BDgt4 = 1;
  else BDgt5 = 1;

if BDLTppmYrs = 0 then BDlt0 = 1;
  else if BDLTppmYrs <=  10.12514  then BDlt1 = 1;
  else if BDLTppmYrs <=  22.08647  then BDlt2 = 1;
  else if BDLTppmYrs <=  49.61442  then BDlt3 = 1;
  else if BDLTppmYrs <=  161.4656  then BDlt4 = 1;
  else BDlt5 = 1;

if STYppmYrs = 0 then STY0 = 1;
  else if STYppmYrs <=  4.476057  then STY1 = 1;
  else if STYppmYrs <=  12.331504  then STY2 = 1;
  else if STYppmYrs <=  28.268034  then STY3 = 1;
  else if STYppmYrs <=  69.018516  then STY4 = 1;
  else STY5 = 1;

if STYpeakYrs = 0 then STYpk0 = 1;
  else if STYpeakYrs <=  11.73973  then STYpk1 = 1;
  else if STYpeakYrs <=  27.93188  then STYpk2 = 1;
  else if STYpeakYrs <=  134.4072  then STYpk3 = 1;
  else if STYpeakYrs <=  1249.582  then STYpk4 = 1;
  else STYpk5 = 1;

if STYGTppmYrs = 0 then STYgt0 = 1;
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   else if STYGTppmYrs <=  0.01811828  then STYgt1 = 1;
   else if STYGTppmYrs <=  0.1081289  then STYgt2 = 1;
   else if STYGTppmYrs <=  1.974963  then STYgt3 = 1;
   else if STYGTppmYrs <=  19.5782600000001  then STYgt4 = 1;
   else STYgt5 = 1;

  if STYLTppmYrs = 0 then STYlt0 = 1;
   else if STYLTppmYrs <=  3.4894936  then STYlt1 = 1;
   else if STYLTppmYrs <=  9.931024  then STYlt2 = 1;
   else if STYLTppmYrs <=  24.322588  then STYlt3 = 1;
   else if STYLTppmYrs <=  57.4921920000002  then STYlt4 = 1;
   else STYlt5 = 1;

  if YSH <=  34.4197125256674  then YSH0 = 1;
   else if YSH <=  42.2318959616701  then YSH1 = 1;
   else if YSH <=  48.6072553045859  then YSH2 = 1;
   else if YSH <=  53.5342915811088  then YSH3 = 1;
   else YSH4 = 1;

  if CalYr <=  1986  then CalYr0 = 1;
   else if CalYr <=  1994  then CalYr1 = 1;
   else if CalYr <=  2000  then CalYr2 = 1;
   else if CalYr <=  2005  then CalYr3 = 1;
   else CalYr4 = 1;

end;

else if "&Response" = 'Lung' then do;

  if BDppmYrs = 0 then BDppmYrsDec=0;
   else if BDppmYrs <=  4.9885386  then BDppmYrsDec = 1.91920632657794;
   else if BDppmYrs <=  13.61353  then BDppmYrsDec = 9.00022129850747;
   else if BDppmYrs <=  28.133337  then BDppmYrsDec = 20.6215873134328;
   else if BDppmYrs <=  48.481998  then BDppmYrsDec = 37.3829222058824;
   else if BDppmYrs <=  71.84389  then BDppmYrsDec = 60.0872658208955;
   else if BDppmYrs <=  118.6872  then BDppmYrsDec = 91.1178074626866;
   else if BDppmYrs <=  178.01417  then BDppmYrsDec = 144.755389705882;
   else if BDppmYrs <=  286.28234  then BDppmYrsDec = 227.895110447761;
   else if BDppmYrs <=  538.226400000001  then BDppmYrsDec = 375.634856716418;
   else BDppmYrsDec = 1529.05046323529;

  if BDppmYrs = 0 then BDppm0=1;
   else if BDppmYrs <=  4.9885386  then BDppm1 = 1;
   else if BDppmYrs <=  13.61353  then BDppm2 = 1;
```

```
  else if BDppmYrs <=  28.133337  then BDppm3 = 1;
  else if BDppmYrs <=  48.481998  then BDppm4 = 1;
  else if BDppmYrs <=  71.84389  then BDppm5 = 1;
  else if BDppmYrs <=  118.6872  then BDppm6 = 1;
  else if BDppmYrs <=  178.01417  then BDppm7 = 1;
  else if BDppmYrs <=  286.28234  then BDppm8 = 1;
  else if BDppmYrs <=  538.226400000001  then BDppm9 = 1;
  else BDppm10 = 1;

if BDpeakYrs = 0 then BDpk0 = 1;
  else if BDpeakYrs <=  79.17451  then BDpk1 = 1;
  else if BDpeakYrs <=  323.241  then BDpk2 = 1;
  else if BDpeakYrs <=  903.0238  then BDpk3 = 1;
  else if BDpeakYrs <=  2626.677  then BDpk4 = 1;
  else BDpk5 = 1;

if BDGTppmYrs = 0 then BDgt0 = 1;
  else if BDGTppmYrs <=  8.638184  then BDgt1 = 1;
  else if BDGTppmYrs <=  29.38556  then BDgt2 = 1;
  else if BDGTppmYrs <=  77.6917  then BDgt3 = 1;
  else if BDGTppmYrs <=  215.5071  then BDgt4 = 1;
  else BDgt5 = 1;

if BDLTppmYrs = 0 then BDlt0 = 1;
  else if BDLTppmYrs <=  5.3308012  then BDlt1 = 1;
  else if BDLTppmYrs <=  16.356084  then BDlt2 = 1;
  else if BDLTppmYrs <=  38.771154  then BDlt3 = 1;
  else if BDLTppmYrs <=  93.325648  then BDlt4 = 1;
  else BDlt5 = 1;

if STYppmYrs = 0 then STY0 = 1;
  else if STYppmYrs <=  3.3638348  then STY1 = 1;
  else if STYppmYrs <=  9.6163752  then STY2 = 1;
  else if STYppmYrs <=  24.225466  then STY3 = 1;
  else if STYppmYrs <=  54.9113120000001  then STY4 = 1;
  else STY5 = 1;

if STYpeakYrs = 0 then STYpk0 = 1;
  else if STYpeakYrs <=  12.247022  then STYpk1 = 1;
  else if STYpeakYrs <=  42.553224  then STYpk2 = 1;
  else if STYpeakYrs <=  119.65658  then STYpk3 = 1;
  else if STYpeakYrs <=  592.438680000002  then STYpk4 = 1;
  else STYpk5 = 1;
```

```
      if STYGTppmYrs = 0 then STYgt0 = 1;
        else if STYGTppmYrs <=  0.032531334  then STYgt1 = 1;
        else if STYGTppmYrs <=  0.185221  then STYgt2 = 1;
        else if STYGTppmYrs <=  2.3016022  then STYgt3 = 1;
        else if STYGTppmYrs <=  18.435362  then STYgt4 = 1;
        else STYgt5 = 1;

      if STYLTppmYrs = 0 then STYlt0 = 1;
        else if STYLTppmYrs <=  3.035305  then STYlt1 = 1;
        else if STYLTppmYrs <=  8.3105626  then STYlt2 = 1;
        else if STYLTppmYrs <=  18.726956  then STYlt3 = 1;
        else if STYLTppmYrs <=  41.863884  then STYlt4 = 1;
        else STYlt5 = 1;

      if YSH <=  26.9344284736482  then YSH0 = 1;
        else if YSH <=  34.560438056126  then YSH1 = 1;
        else if YSH <=  41.5912388774812  then YSH2 = 1;
        else if YSH <=  48.145106091718  then YSH3 = 1;
        else YSH4 = 1;

      if CalYr <=  1981  then CalYr0 = 1;
        else if CalYr <=  1988  then CalYr1 = 1;
        else if CalYr <=  1995  then CalYr2 = 1;
        else if CalYr <=  2002  then CalYr3 = 1;
        else CalYr4 = 1;

    end;


     Plant0=0; Plant1=0; Plant2=0; Plant3=0; Plant4=0; Plant5=0;
     If plant = 1 Then Plant0 = 1;
        else if plant = 3 Then Plant1 = 1;
        else if plant = 4 Then Plant2 = 1;
        else if plant = 6 Then Plant3 = 1;
        else if plant = 7 Then Plant4 = 1;
        else if plant = 8 Then Plant5 = 1;

  Keep FUstartAge FUendAge &Response &dMetric &Covariates;
run;

%Mend FitPH;
*================================================================================
====================;
```

A2.3 OneCovX2020PH-Shared.LST

Note – The text below corresponds to the SAS file "OneCovX2020PH-Shared.LST" consisting of output code containing the results of the SAS run of the six models listed in Table 13 of Valdez-Flores et al. (2022).

Sex = M,F' 1
Endpoint = Leukemia BDppmYrs-Years with Age as index variable
Covariates:
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The FREQ Procedure

Leukemia	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	20955	99.37	20955	99.37
1	52	0.25	21007	99.62
2	67	0.32	21074	99.94
3	13	0.06	21087	100.00

Plant	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1564	7.42	1564	7.42
3	2462	11.68	4026	19.09
4	2848	13.51	6874	32.60
6	2928	13.89	9802	46.48
7	7044	33.40	16846	79.89
8	4241	20.11	21087	100.00

SexN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4508	21.38	4508	21.38
1	16579	78.62	21087	100.00

RaceN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	18674	88.56	18674	88.56

2	2413	11.44	21087	100.00

Sex = M,F' 2
Endpoint = Leukemia BDppmYrs-Years with Age as index variable
Covariates:
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The PHREG Procedure

Model Information

Data Set	WORK.COXDATA
Dependent Variable	FUstartAge
Dependent Variable	FUendAge
Censoring Variable	Leukemia
Censoring Value(s)	0
Ties Handling	EXACT

Number of Observations Read	21087
Number of Observations Used	21087

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
21087	132	20955	99.37

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2384.194	2377.395
AIC	2384.194	2379.395
SBC	2384.194	2382.278

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	6.7991	1	0.0091
Score	12.9275	1	0.0003
Wald	11.2171	1	0.0008

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0002808	0.0000838	11.2171	0.0008	1.000

Sex = M,F' 3
Endpoint = Bladder BDppmYrs-Years with Age as index variable
Covariates:
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The FREQ Procedure

Bladder	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	20992	99.55	20992	99.55
1	90	0.43	21082	99.98
2	5	0.02	21087	100.00

Plant	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1564	7.42	1564	7.42
3	2462	11.68	4026	19.09
4	2848	13.51	6874	32.60
6	2928	13.89	9802	46.48
7	7044	33.40	16846	79.89
8	4241	20.11	21087	100.00

SexN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4508	21.38	4508	21.38
1	16579	78.62	21087	100.00

RaceN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	18674	88.56	18674	88.56
2	2413	11.44	21087	100.00

Sex = M,F' 4
Endpoint = Bladder BDppmYrs-Years with Age as index variable
Covariates:
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The PHREG Procedure

Model Information

Data Set	WORK.COXDATA
Dependent Variable	FUstartAge
Dependent Variable	FUendAge
Censoring Variable	Bladder
Censoring Value(s)	0
Ties Handling	EXACT

Number of Observations Read	21087
Number of Observations Used	21087

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
21087	95	20992	99.55

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1608.352	1599.817
AIC	1608.352	1601.817
SBC	1608.352	1604.371

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	8.5348	1	0.0035
Score	18.5580	1	<.0001
Wald	15.0853	1	0.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0003159	0.0000813	15.0853	0.0001	1.000

Sex = M,F' 5
Endpoint = LeukBlad BDppmYrs-Years with Age as index variable
Covariates:
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The FREQ Procedure

LeukBlad	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	20861	98.93	20861	98.93
1	226	1.07	21087	100.00

Plant	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1564	7.42	1564	7.42
3	2462	11.68	4026	19.09
4	2848	13.51	6874	32.60
6	2928	13.89	9802	46.48
7	7044	33.40	16846	79.89
8	4241	20.11	21087	100.00

SexN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4508	21.38	4508	21.38
1	16579	78.62	21087	100.00

RaceN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	18674	88.56	18674	88.56
2	2413	11.44	21087	100.00

Sex = M,F' 6
Endpoint = LeukBlad BDppmYrs-Years with Age as index variable
Covariates:
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The PHREG Procedure

Model Information

Data Set	WORK.COXDATA
Dependent Variable	FUstartAge
Dependent Variable	FUendAge
Censoring Variable	LeukBlad
Censoring Value(s)	0
Ties Handling	EXACT

Number of Observations Read	21087
Number of Observations Used	21087

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
21087	226	20861	98.93

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	3975.348	3959.979
AIC	3975.348	3961.979
SBC	3975.348	3965.400

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	15.3690	1	<.0001
Score	31.2318	1	<.0001
Wald	26.2842	1	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0002991	0.0000583	26.2842	<.0001	1.000

Sex = M,F' 7
Endpoint = Leukemia BDppmYrs-Years with Age as index variable
Covariates: BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The FREQ Procedure

Leukemia	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	20955	99.37	20955	99.37
1	52	0.25	21007	99.62
2	67	0.32	21074	99.94
3	13	0.06	21087	100.00

Plant	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1564	7.42	1564	7.42
3	2462	11.68	4026	19.09
4	2848	13.51	6874	32.60
6	2928	13.89	9802	46.48
7	7044	33.40	16846	79.89
8	4241	20.11	21087	100.00

SexN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4508	21.38	4508	21.38
1	16579	78.62	21087	100.00

RaceN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	18674	88.56	18674	88.56
2	2413	11.44	21087	100.00

Sex = M,F' 8
Endpoint = Leukemia BDppmYrs-Years with Age as index variable
Covariates: BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The PHREG Procedure

Model Information

Data Set	WORK.COXDATA
Dependent Variable	FUstartAge
Dependent Variable	FUendAge
Censoring Variable	Leukemia
Censoring Value(s)	0
Ties Handling	EXACT

Number of Observations Read	21087
Number of Observations Used	21087

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
21087	132	20955	99.37

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2384.194	2340.413
AIC	2384.194	2352.413
SBC	2384.194	2369.709

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	43.7819	6	<.0001
Score	51.4912	6	<.0001
Wald	45.3329	6	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0001316	0.0001079	1.4870	0.2227	1.000
BDpk1	1	0.36762	0.28728	1.6374	0.2007	1.444
BDpk2	1	1.23058	0.29123	17.8539	<.0001	3.423
BDpk3	1	0.62796	0.28993	4.6912	0.0303	1.874
BDpk4	1	1.50661	0.29871	25.4391	<.0001	4.511
BDpk5	1	1.21407	0.29354	17.1064	<.0001	3.367
BDpk0	0	0	.	.	.	.

Sex = M,F' 9
Endpoint = Bladder BDppmYrs-Years with Age as index variable
Covariates: SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The FREQ Procedure

Bladder	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	20992	99.55	20992	99.55
1	90	0.43	21082	99.98
2	5	0.02	21087	100.00

Plant	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1564	7.42	1564	7.42
3	2462	11.68	4026	19.09
4	2848	13.51	6874	32.60
6	2928	13.89	9802	46.48
7	7044	33.40	16846	79.89
8	4241	20.11	21087	100.00

SexN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4508	21.38	4508	21.38
1	16579	78.62	21087	100.00

RaceN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	18674	88.56	18674	88.56
2	2413	11.44	21087	100.00

Sex = M,F' 10
Endpoint = Bladder BDppmYrs-Years with Age as index variable
Covariates: SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The PHREG Procedure

Model Information

Data Set	WORK.COXDATA
Dependent Variable	FUstartAge
Dependent Variable	FUendAge
Censoring Variable	Bladder
Censoring Value(s)	0
Ties Handling	EXACT

Number of Observations Read	21087
Number of Observations Used	21087

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
21087	95	20992	99.55

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1608.352	1588.777
AIC	1608.352	1592.777
SBC	1608.352	1597.885

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	19.5746	2	<.0001
Score	25.8726	2	<.0001
Wald	21.4855	2	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0002802	0.0000852	10.8192	0.0010	1.000
SexN	1	0.98751	0.33630	8.6226	0.0033	2.685

Sex = M,F' 11
Endpoint = LeukBlad BDppmYrs-Years with Age as index variable
Covariates: BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0 SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The FREQ Procedure

LeukBlad	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	20861	98.93	20861	98.93
1	226	1.07	21087	100.00

Plant	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	1564	7.42	1564	7.42
3	2462	11.68	4026	19.09
4	2848	13.51	6874	32.60
6	2928	13.89	9802	46.48
7	7044	33.40	16846	79.89
8	4241	20.11	21087	100.00

SexN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4508	21.38	4508	21.38
1	16579	78.62	21087	100.00

RaceN	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	18674	88.56	18674	88.56
2	2413	11.44	21087	100.00

Sex = M,F' 12
Endpoint = LeukBlad BDppmYrs-Years with Age as index variable
Covariates: BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0 SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

The PHREG Procedure

Model Information

Data Set	WORK.COXDATA
Dependent Variable	FUstartAge
Dependent Variable	FUendAge
Censoring Variable	LeukBlad
Censoring Value(s)	0
Ties Handling	EXACT

Number of Observations Read	21087
Number of Observations Used	21087

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
21087	226	20861	98.93

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	3975.348	3907.404
AIC	3975.348	3921.404
SBC	3975.348	3945.348

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	67.9441	7	<.0001
Score	79.0626	7	<.0001
Wald	69.9901	7	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0001726	0.0000725	5.6670	0.0173	1.000
BDpk1	1	0.07893	0.22583	0.1222	0.7267	1.082
BDpk2	1	0.80479	0.23427	11.8017	0.0006	2.236
BDpk3	1	0.32162	0.22401	2.0614	0.1511	1.379
BDpk4	1	1.04061	0.24030	18.7533	<.0001	2.831
BDpk5	1	0.88996	0.22441	15.7280	<.0001	2.435
BDpk0	0	0	.	.	.	.
SexN	1	0.57499	0.22578	6.4857	0.0109	1.777

Attachment 3. Checking the Proportional Hazard assumption of the BD final models

July 2, 2024

The proportional hazards model (PHM) assumes that the hazards of two individuals is a constant over time. The PHM, however, can be generalized to handle nonproportional hazards as in the case of time-dependent variables (e.g., cumulative BD ppm-years). Although the PHM assumptions are often satisfied for time-independent covariates, sometimes it may be necessary to test whether the assumptions of the PHM are satisfied. The analyses presented here were run to address some of the following observations made by an expert:

The Cox proportional hazards model makes several assumptions. Thus, it is important to assess whether a fitted Cox regression model adequately describes the data. Here, we'll discuss three types of diagnostics for the Cox model:

- Testing the proportional hazards assumption.
- Examining influential observations (or outliers).
- Detecting nonlinearity in relationship between the log hazard and the covariates.

In order to check these model assumptions, *Residuals* method are used. The common residuals for the Cox model include:

- *Schoenfeld residuals* to check the proportional hazards assumption
- *Martingale residual* to assess nonlinearity
- *Deviance residual* (symmetric transformation of the Martinguale residuals), to examine influential observations".

(There may be other ways to test the CPH assumptions that I am unaware of.) While I think it is fine to "describe potential future refinements to modeling and the need for guidance development", I see no reason to ignore conducting tests of the CPH assumptions, especially since they may turn out to be confirmed, strengthening the results of the modeling"

If the model includes time-dependent variables (e.g., cumulative BD ppm-years) the assumption of proportional hazards model does not apply but the partial likelihood approach developed for the PHM can still be used. This is because time-dependent variables change at different times for different individuals resulting in time-varying ratios of hazards for different individuals, i.e., hazard ratios do not remain constant over time. Thus, the model we used for BD is not a PHM, but it is customarily called PHM because the partial likelihood method associated with the PHM can still be used to estimate model parameters.

Because of the time-dependent covariates, it is difficult to check the PH assumption. Paul Allison, an expert in PH modeling, writes: "But suppose you don't have any time-dependent covariates. How do you know whether your data satisfy the PH assumption, and what happens if the assumption is violated? Although these are legitimate questions, I personally believe that concern about the PH assumption is often

excessive. Every model embodies many assumptions, some more questionable or consequential than others. The reason people focus so much attention on the PH assumption is that the model is named for that property."

Allison continues saying: "To put this issue in perspective, you need to understand that violations of the PH assumption are equivalent to interactions between one or more covariates and time. That is, the PH model assumes that the effect of each covariate is the same at all points in time. If the effect of a variable varies with time, the PH assumption is violated for that variable. It's unlikely that the PH assumption is ever exactly satisfied, but that's true of nearly all statistical assumptions. If we estimate a PH model when the assumption is violated for some variable (thereby suppressing the interaction), then the coefficient that we estimate for that variable is a sort of average effect over the range of times observed in the data. Is this so terrible? In fact, researchers suppress interactions all the time when they estimate regression models. In models with even a moderately large number of variables, no one tests for all the possible 2-way interactions—there are just too many of them."
Allison, however, shows one method that allows to check the PH assumption using martingale residuals or Schoenfeld residuals, but that method can be used only if the model does not include time-dependent variables like cumulative BD ppm-years.
Allison recommends to explicitly test an interaction effect between time and the covariate of interest to check the PH assumption in a PHM that include time-dependent variables. If the interaction is statistically significant, then the PH assumption does not apply to the covariate of interest.
The BD PH models include the time-dependent variable BD ppm-years. Though the PH assumption for other time-independent variables was not checked, here we re-run the models including an interaction effect to determine whether the PH assumption was satisfied for time-independent covariates included in the final models presented in Table 11 of the BD manuscript (reproduced here for convenience).
Table 11. Estimates of the average environmental BD exposure concentrations (ppm) for a lifetime of exposure (starting at birth) corresponding to an excess risks of 1 in a million by age 70 years using the maximum likelihood estimate (EC) of the Cox proportional hazards log-linear models and its 95% lower and upper confidence limits (LEC, UEC): Model with BD ppm-years as the predictor variable with no covariates and with statistically significant covariates for leukemia, bladder/urinary and the aggregate leukemia or bladder/urinary cancer

Endpoint	Covariate[1]	Slope[2] (MLE)	Slope (Std Dev)	Stat. Sig.[3] of Slope	Lag[4]	Average Environmental Concentration (ppm)[5]
						EC (LEC, UEC)
Model not adjusted for the effect of covariates						
Leukemia	None	0.0002808	0.0000838	SS(1%)	0	0.0127 (0.0085, 0.0250)

Bladder/ Urinary	None	0.0003159	0.0000813	SS(1%)	0	0.0187 (0.0132, 0.0325)
Aggregate (Leukemia or Bladder/ Urinary)	None	0.0002991	0.0000583	SS(1%)	0	0.0075 (0.0056, 0.0110)
Model adjusted for statistically significant covariates						
Leukemia	BD HITs	0.0001316	0.0001079	NS	0	0.0271 (0.0116, n/a[6])
Bladder/ Urinary	Sex	0.0002802	0.0000852	SS(5%)	0	0.0211 (0.0141, 0.4224)
Aggregate (Leukemia or Bladder/ Urinary)	BD HITs and Sex	0.0001726	0.0000725	SS(5%)	0	0.0129 (0.0076, 0.0418)

[1]Covariate is a non-exposure or exposure covariate that results in a statistically significant (at the 1% significance level) increase in the maximum likelihood over the maximum likelihood for the model with only cumulative BD ppm-years. Covariates are listed in the order from most to least significant improvement. (Adjusting for Sex as another covariate, resulted in smaller slope estimates for BD ppm-years: data not shown.)
[2]Slope is the coefficient of cumulative BD ppm-years in the Cox model.
[3]SS (1%) implies that the slope is statistically significantly different than zero (at the 1% significance level); SS (5%) implies that the slope is statistically significantly different than zero (at the 5% significance level); NS implies that the slope is not statistically significantly different than zero (at the 5% significance level). Based on likelihood ratio test.
[4]Lag in years. Statistically significant (at the 1% significance level) improvement in the maximum likelihood.
[5]Environmental exposure corresponds to the persons being exposed continuously from birth until the end of calculations (70 years). Added risks are calculated using life-table methodology with 2019 U.S. mortality rates and 2017 U.S. survival probabilities.
[6]n/a means that the upper bound of the EC cannot be estimated because the lower bound on the slope for BD ppm-years is zero or negative.

The first four models in Table 11 include only time dependent variables (BD ppm-years and BD HITs). Thus, testing for the PH assumption is not necessary, as discussed above.
For Bladder/Urinary adjusted for sex the PH assumption was checked by including an interaction effect between time and sex.
Following Allison's recommendation, an interaction effect between time and sex was added to the PHM. If the interaction effect is statistically significant, then the PH assumption does not apply to the covariate Sex.
Appendix I lists the results for Bladder/Urinary adjusted for Sex and Aggregate (Leukemia or Bladder/ Urinary) adjusted for BD HITs and Sex. Sex has Wald-based p-values of 0.0033 and 0.0109 for Bladder/Urinary and Aggregate (Leukemia or Bladder/ Urinary), respectively.

Appendix II lists the results for Bladder/Urinary adjusted for Sex and an interaction of time*Sex and Aggregate (Leukemia or Bladder/ Urinary) adjusted for BD HITs, Sex and an interaction of time*Sex. Sex has Wald-based p-values of 0.0776 and 0.0516 for Bladder/Urinary and Aggregate (Leukemia or Bladder/ Urinary), respectively. The interaction time*Sex has Wald-based p-values of 0.9331 and 0.6741 for Bladder/Urinary and Aggregate (Leukemia or Bladder/ Urinary), respectively. These high p-values for the interaction time*Sex indicates that the PH assumption effect of the covariate Sex cannot be rejected. It is noteworthy that the MLE parameter estimates for BD ppm-years where essentially unchanged after including the interaction effect (2.816E-04 and 1.747E-04 for Bladder/Urinary and Aggregate (Leukemia or Bladder/ Urinary), respectively) when compared to the MLE parameters for the same endpoints listed in Table 11.
The final PH models presented in the BD publication do satisfy the PH assumptions for the time-independent covariate included in the models.

Reference

Allison, Paul D. 2010. Survival Analysis Using SAS, A Practical guide, second edition. SAS Institute Inc., Cary, NC, USA.

Appendix I. SAS output of original models (with no interaction effects).

Sex = M,F'
Endpoint = Bladder BDppmYrs-Years with Age as index variable
Covariates: SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1608.352	1588.777
AIC	1608.352	1592.777
SBC	1608.352	1597.885

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	19.5746	2	<.0001
Score	25.8726	2	<.0001
Wald	21.4855	2	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0002802	0.0000852	10.8192	0.0010	1.000
SexN	1	0.98751	0.33630	8.6226	0.0033	2.685

Sex = M,F'
Endpoint = LeukBlad BDppmYrs-Years with Age as index variable
Covariates: BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0 SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	3975.348	3907.404
AIC	3975.348	3921.404
SBC	3975.348	3945.348

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	67.9441	7	<.0001
Score	79.0626	7	<.0001
Wald	69.9901	7	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0001726	0.0000725	5.6670	0.0173	1.000
BDpk1	1	0.07893	0.22583	0.1222	0.7267	1.082
BDpk2	1	0.80479	0.23427	11.8017	0.0006	2.236
BDpk3	1	0.32162	0.22401	2.0614	0.1511	1.379
BDpk4	1	1.04061	0.24030	18.7533	<.0001	2.831
BDpk5	1	0.88996	0.22441	15.7280	<.0001	2.435
BDpk0	0	0	.	.	.	.
SexN	1	0.57499	0.22578	6.4857	0.0109	1.777

Appendix II. SAS output of models including an interaction effect to test the proportional hazards assumption.

Sex = M,F'
Endpoint = Bladder BDppmYrs-Years with Age as index variable
Covariates: SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1608.352	1588.770
AIC	1608.352	1594.770
SBC	1608.352	1602.432

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	19.5816	3	0.0002
Score	25.8795	3	<.0001
Wald	21.4917	3	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0002810	0.0000857	10.7462	0.0010	1.000
SexN	1	1.02747	0.58215	3.1151	0.0776	2.794
timeXsexN	1	-2.6321E-6	0.0000313	0.0071	0.9331	1.000

Sex = M,F'
Endpoint = LeukBlad BDppmYrs-Years with Age as index variable
Covariates: BDpk1 BDpk2 BDpk3 BDpk4 BDpk5 BDpk0 SexN
Lag = 0 and also exclude exposures that occurred -1 or more years ago

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	3975.348	3907.228
AIC	3975.348	3923.228
SBC	3975.348	3950.592

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	68.1202	8	<.0001
Score	79.1930	8	<.0001
Wald	70.1226	8	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
BDppmYrs	1	0.0001747	0.0000727	5.7686	0.0163	1.000
BDpk1	1	0.08134	0.22588	0.1297	0.7188	1.085
BDpk2	1	0.80661	0.23427	11.8546	0.0006	2.240
BDpk3	1	0.32588	0.22422	2.1125	0.1461	1.385
BDpk4	1	1.04671	0.24064	18.9201	<.0001	2.848
BDpk5	1	0.90128	0.22596	15.9092	<.0001	2.463
BDpk0	0	0	.	.	.	.
SexN	1	0.69007	0.35459	3.7873	0.0516	1.994
timeXsexN	1	-8.553E-6	0.0000203	0.1769	0.6741	1.000

Appendix D. Monte Carlo Assessment of Interspecies Extrapolation Calculations for 1,3-Butadiene

A 1-dimensional Monte Carlo assessment was conducted for the interspecies extrapolation calculations used to support noncancer risk assessment for 1,3-butadiene (BD) as described in Kirman et al. (2022). This included two separate calculations for interspecies extrapolation: (1) for ovarian atrophy effects, calculations reflect species differences in the internal dose of the causative agent (diepoxide metabolite, DEB); (2) for fetal body weight effects, calculations reflect species differences in the internal doses of three epoxide metabolites of BD (EB, DEB, EBD) and metabolite differences in toxic potency as described in Kirman et al. (2022). A list of the parameter assumptions is included in **Table C-1**. Simulations were performed using the XLRisk add-in for Microsoft Excel, using 10,000 iterations with Latin hypercube sampling.

Table C-1. Monte Carlo Parameter Distribution for Interspecies Adjustment Calculations

Parameter	Distribution	Source
EB internal dose in female mice	RiskNormal(13,1)	Based upon the mean and standard deviations reported by Motwani and Tornqvist (2014; Table 3). Distribution reflects variation across individual animals and humans
DEB internal dose in female mice	RiskNormal(27,3.5)	
EBD internal dose in female mice	RiskNormal(266,35.5)	
EB internal dose in female rat	RiskNormal(0.77,0.058)	
DEB internal dose in female rats	RiskNormal(1.45,0.12)	
EBD internal dose in female rats	RiskNormal(19,1.2)	
EB internal dose in humans	RiskNormal(0.11,0.014)	
DEB internal dose in humans	RiskNormal(0.024,0.037)	
EBD internal dose in humans	RiskNormal(52,6.4)	
Cytotoxic potency of DEB relative to EB	RiskPert(32.9,171,670)	Based upon the minimum, mean, and maximum values reported by Kirman et al. (2022; Table 5); Distribution reflects variation across data sets
Cytotoxic potency of EBD relative to EB	RiskPert(0,0.578,1.04)	

Resulting distributions for the two interspecies extrapolations are provided in **Table C-2**, with sensitivity analyses provided in **Table C-3**.

Table C-2. Distributions for Interspecies Extrapolations for BD Noncancer Risk Assessment

	Data-Derived Extrapolation Factor for Fetal Body Weight Changes (all 3 metabolites contributing)				Data-Derived Extrapolation Factor for Ovarian Atrophy (only DEB contributing)			
Percentiles	Human: Mouse	Normalized*	Human: Rat	Normalized*	Human: Mouse	Normalized*	Human: Rat	Normalized*
0.01	1.8E-03	3.1E-01	3.4E-02	2.6E-01	6.0E-04	6.9E-01	1.2E-02	7.3E-01
0.025	2.1E-03	3.7E-01	3.9E-02	3.1E-01	6.4E-04	7.3E-01	1.2E-02	7.7E-01
0.05	2.4E-03	4.2E-01	4.5E-02	3.6E-01	6.7E-04	7.8E-01	1.3E-02	8.1E-01
0.075	2.7E-03	4.7E-01	5.0E-02	3.9E-01	7.0E-04	8.0E-01	1.4E-02	8.3E-01
0.1	2.9E-03	5.1E-01	5.4E-02	4.2E-01	7.2E-04	8.2E-01	1.4E-02	8.5E-01
0.125	3.0E-03	5.4E-01	5.7E-02	4.5E-01	7.3E-04	8.4E-01	1.4E-02	8.7E-01
0.15	3.2E-03	5.7E-01	6.1E-02	4.8E-01	7.5E-04	8.6E-01	1.4E-02	8.9E-01
0.175	3.4E-03	6.1E-01	6.4E-02	5.0E-01	7.6E-04	8.7E-01	1.5E-02	9.0E-01
0.2	3.6E-03	6.4E-01	6.7E-02	5.3E-01	7.7E-04	8.9E-01	1.5E-02	9.1E-01
0.225	3.8E-03	6.7E-01	7.0E-02	5.5E-01	7.8E-04	9.0E-01	1.5E-02	9.2E-01
0.25	3.9E-03	7.0E-01	7.3E-02	5.7E-01	7.9E-04	9.1E-01	1.5E-02	9.3E-01
0.275	4.1E-03	7.3E-01	7.6E-02	6.0E-01	8.0E-04	9.2E-01	1.5E-02	9.4E-01
0.3	4.3E-03	7.6E-01	7.8E-02	6.2E-01	8.1E-04	9.4E-01	1.5E-02	9.5E-01
0.325	4.4E-03	7.8E-01	8.1E-02	6.4E-01	8.2E-04	9.5E-01	1.6E-02	9.6E-01
0.35	4.6E-03	8.1E-01	8.4E-02	6.6E-01	8.3E-04	9.6E-01	1.6E-02	9.7E-01
0.375	4.7E-03	8.4E-01	8.7E-02	6.9E-01	8.4E-04	9.7E-01	1.6E-02	9.8E-01
0.4	4.9E-03	8.7E-01	9.0E-02	7.1E-01	8.5E-04	9.8E-01	1.6E-02	9.9E-01
0.425	5.1E-03	9.0E-01	9.3E-02	7.3E-01	8.6E-04	9.9E-01	1.6E-02	1.0E+00
0.45	5.2E-03	9.3E-01	9.6E-02	7.6E-01	8.7E-04	1.0E+00	1.6E-02	1.0E+00
0.475	5.4E-03	9.6E-01	9.9E-02	7.8E-01	8.8E-04	1.0E+00	1.6E-02	1.0E+00
0.5	5.6E-03	9.9E-01	1.0E-01	8.1E-01	8.9E-04	1.0E+00	1.7E-02	1.0E+00
0.525	5.8E-03	1.0E+00	1.1E-01	8.4E-01	9.0E-04	1.0E+00	1.7E-02	1.0E+00
0.55	6.0E-03	1.1E+00	1.1E-01	8.7E-01	9.1E-04	1.0E+00	1.7E-02	1.0E+00
0.575	6.3E-03	1.1E+00	1.1E-01	9.0E-01	9.2E-04	1.1E+00	1.7E-02	1.0E+00
0.6	6.5E-03	1.2E+00	1.2E-01	9.3E-01	9.3E-04	1.1E+00	1.7E-02	1.1E+00
0.625	6.7E-03	1.2E+00	1.2E-01	9.7E-01	9.4E-04	1.1E+00	1.7E-02	1.1E+00
0.65	7.0E-03	1.2E+00	1.3E-01	1.0E+00	9.5E-04	1.1E+00	1.7E-02	1.1E+00
0.675	7.3E-03	1.3E+00	1.3E-01	1.0E+00	9.6E-04	1.1E+00	1.8E-02	1.1E+00
0.7	7.7E-03	1.4E+00	1.4E-01	1.1E+00	9.7E-04	1.1E+00	1.8E-02	1.1E+00
0.725	8.0E-03	1.4E+00	1.5E-01	1.1E+00	9.8E-04	1.1E+00	1.8E-02	1.1E+00
0.75	8.4E-03	1.5E+00	1.5E-01	1.2E+00	1.0E-03	1.1E+00	1.8E-02	1.1E+00
0.775	8.9E-03	1.6E+00	1.6E-01	1.3E+00	1.0E-03	1.2E+00	1.8E-02	1.1E+00
0.8	9.4E-03	1.7E+00	1.7E-01	1.3E+00	1.0E-03	1.2E+00	1.9E-02	1.1E+00

0.825	1.0E-02	1.8E+00	1.8E-01	1.4E+00	1.0E-03	1.2E+00	1.9E-02	1.2E+00
0.85	1.1E-02	1.9E+00	1.9E-01	1.5E+00	1.1E-03	1.2E+00	1.9E-02	1.2E+00
0.875	1.1E-02	2.0E+00	2.1E-01	1.6E+00	1.1E-03	1.2E+00	1.9E-02	1.2E+00
0.9	1.3E-02	2.3E+00	2.3E-01	1.8E+00	1.1E-03	1.3E+00	2.0E-02	1.2E+00
0.925	1.4E-02	2.5E+00	2.5E-01	2.0E+00	1.1E-03	1.3E+00	2.0E-02	1.2E+00
0.95	1.6E-02	2.8E+00	2.9E-01	2.3E+00	1.2E-03	1.4E+00	2.1E-02	1.3E+00
0.975	2.0E-02	3.5E+00	3.5E-01	2.8E+00	1.3E-03	1.4E+00	2.2E-02	1.3E+00
0.99	2.4E-02	4.3E+00	4.3E-01	3.4E+00	1.4E-03	1.6E+00	2.3E-02	1.4E+00

*Values were normalized by dividing by the deterministic nominal values used in Kirman et al. (2022) of 0.00563, 0.127, 0.00087, and 0.0162, respectively.

Table C-3. Sensitivity Analysis Results (correlation coefficients between parameters and results)

Noncancer Endpoint	Parameters	Human:Mouse Extrapolation	Human:Rat Extrapolation
Fetal Body Weight Changes	Mouse internal dose of EB	-1.8E-03	
	Mouse internal dose of DEB	-1.9E-01	
	Mouse internal dose of EBD	8.9E-03	
	Rat internal dose of EB		2.9E-03
	Rat internal dose of DEB		-1.2E-01
	Rat internal dose of EBD		-1.7E-02
	Human internal dose of EB	3.5E-03	1.1E-03
	Human internal dose of DEB	2.4E-02	3.0E-02
	Human internal dose of EBD	1.6E-01	1.7E-01
	DEB toxic potency relative to EB	-6.6E-01	-6.7E-01
	EBD toxic potency relative to EB	4.6E-01	4.7E-01
Ovarian Atrophy	Mouse internal dose of DEB	-7.7E-01	
	Rat internal dose of DEB		-6.1E-01
	Human internal dose of DEB	6.2E-01	7.9E-01