White Paper: Updated Hazard Assessment with Responses to EPA Questions

Prepared for:
American Chemistry Council
1,3-Butadiene TSCA Risk Evaluation Consortium

Prepared by:

August 15, 2024

Executive Summary

- 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 ES-1**). 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).

Table ES-1. Summary of Recommended 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 (**Table 2**)	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} (**Table 4**)	Valdez-Flores et al. (2022)
Noncancer Reference Concentration, Short-term/ Subchronic (**Table 6**)	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	Kirman et al. (2022)

					considered in **Table 6** Alternative uncertainty factor values based on human variation data (e.g., Boysen et al. 2022) are also discussed in Section 3.3	
Noncancer Reference Concentration, Long-term/ Chronic (**Table 6**)	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 in **Table 6** Alternative value for UFh based on new human variation information (Boysen et al. 2022) are also discussed in Section 3.3.	Kirman et al. (2022)

1. Introduction

- In conducting risk assessments for chemicals under TSCA, USEPA is required to meet scientific standards for best available science, utilizing a weight of scientific evidence approach.
- The latest toxicity review, which included the derivation of toxicity values (cancer unit risk and noncancer reference values), was prepared by USEPA in 2002 and does not represent the best available science for 1,3-butadiene (BD).
- BD is a data-rich chemical for which there has been considerable improvement and update in our understanding of the toxicokinetics, toxicity, and carcinogenicity over the past two decades.
- Efforts have been taken to derive and publish toxicity values for BD using NAMs as summarized below.

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 1**).
    - 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 1. 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** do not reflect the scientific weight of evidence, they are not recommended for use in human health risk assessment of BD exposures under TSCA.

3. Updated Assessments Have Been Conducted and Published for BD

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 2**).
    - 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 2**) 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. 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 – 0.00013)
Leukemia	None	0.0127 (0.0085 – 0.025)	0.000079 (0.000040 – 0.00012)
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

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**).

Table 3. 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 4**. 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).

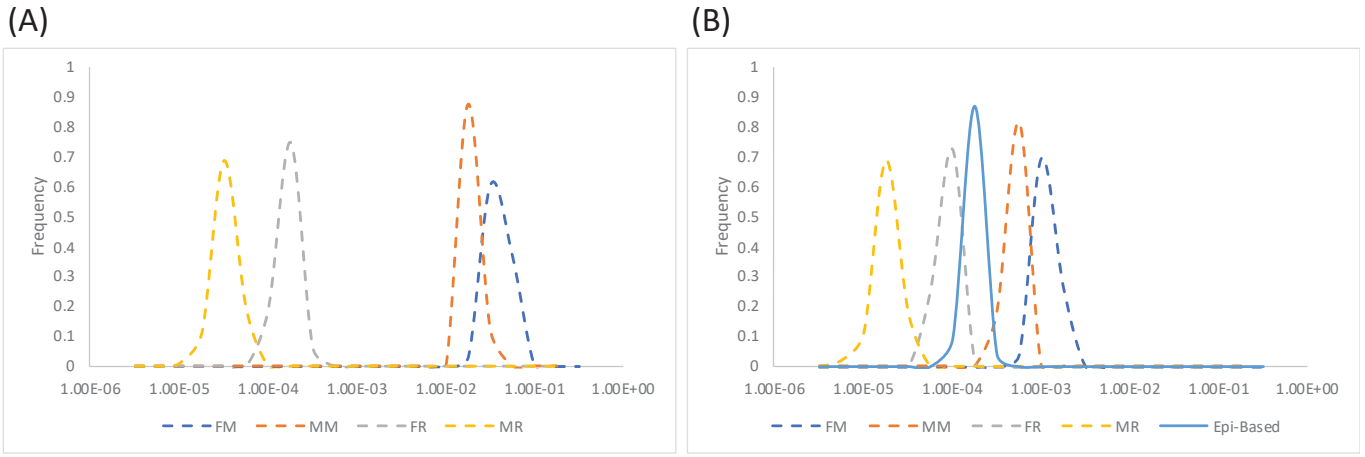
Table 4. Summary of Rodent-Based Unit Risk Values for BD (Kirman and Hays, 2022)

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 2**).
- Accounting for species differences in the metabolic activation of BD results in improved concordance of potency estimates for BD (**Figure 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 1. Concordance of unit risk distributions: (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).



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 5**). 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 5. 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 1**) are provided in **Table 6**. 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 6. Summary of Rodent-Based Reference Concentrations (Kirman et al. 2022)

Parameter	**Subchronic RfCs Based on Fetal Body Weight Changes**			**Chronic RfCs Based on Ovarian Atropy**		
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] (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 6**, 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 6**.
    - 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).

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 1**), 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.

4. Response to EPA Questions and Requests During May 28th Webinar

A webinar was held on May 28, 2024 to provide USEPA with details on hazard assessments of Valdez-Flores et al. (2022) for cancer endpoints, and of Kirman et al. (2022) for the noncancer endpoints of 1,3-butadiene (BD). The data and methods of these assessments are currently being updated and integrated into SciPinion's independent human health risk assessment for BD, which is ongoing. During this webinar, USEPA posed several questions/requests related to the following topic areas:

- Mode of action (MOA)/key events for the noncancer risk assessment to support data-derived extrapolation factor (DDEF) derivation;
- Charge questions provided to SciPinion's science advisory panel;
- Calculation details for human equivalent concentration values used in the benchmark dose analyses for noncancer endpoints; and

- Additional information on modeling of the styrene-butadiene rubber (SBR) worker cohort in SAS.

The text below provides SciPinion's initial responses to these questions/requests.

4.1 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.

4.1.1 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.

4.1.1.1 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).

4.1.1.2 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 8** 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 will be included as an appendix to SciPinion's human health risk assessment (which will be submitted for publication approximately within the next two months), 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).

4.1.1.3 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.

4.1.1.4 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.

4.1.2 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

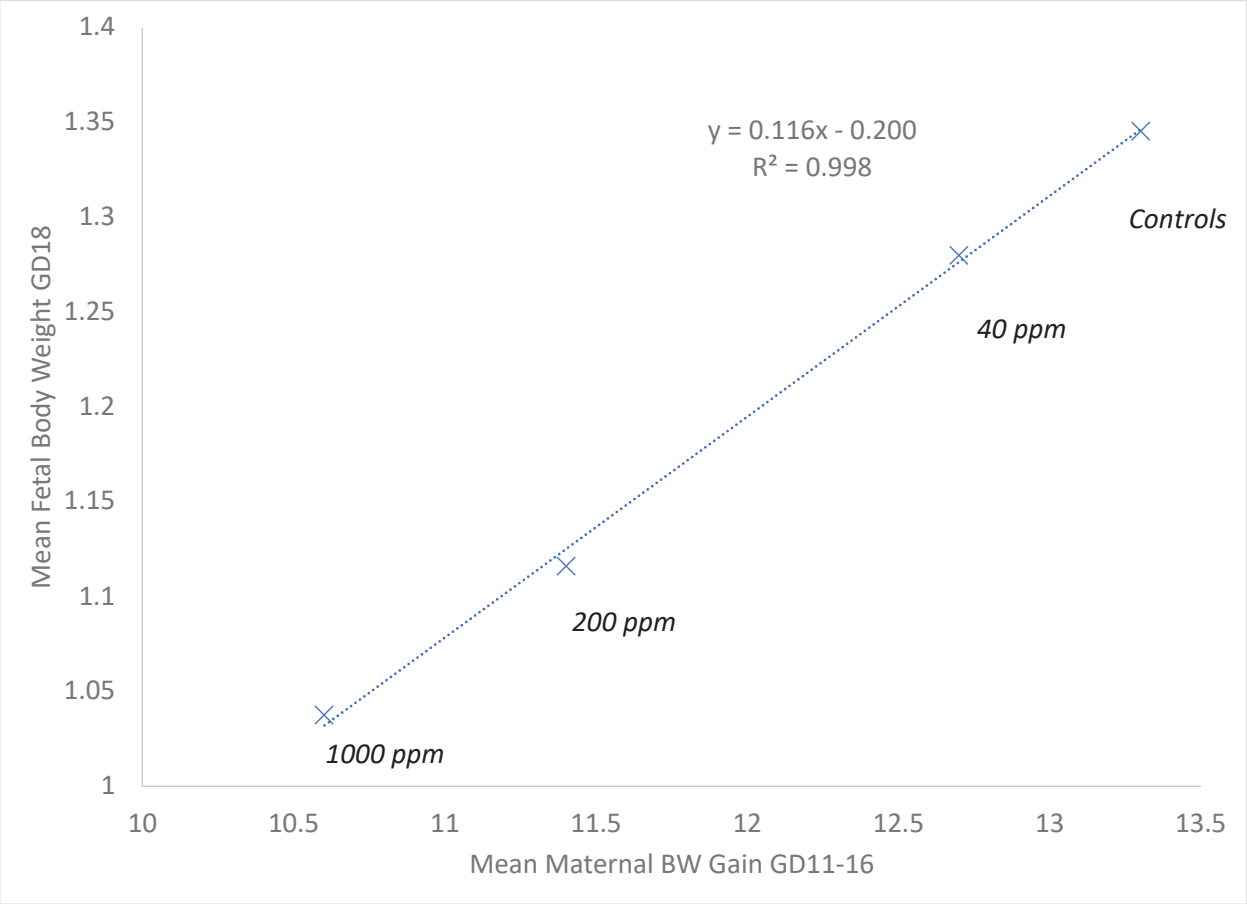
Information on the MOA for the effects on BD exposure on fetal body weight in mice are limited. Key events (KEs) for BD's proposed MOA in fetal body weight in mice are summarized below. As noted above for the ovarian effects of BD, because metabolism is an important determinant of BD's toxicity, and 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)



4.1.2.2 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 7** 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.

4.1.2.3 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.

4.1.2.4 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.

4.2 Charge Questions to Science Advisory Panel

We will be including a complete set of charge questions, review materials, and individual responses from SciPinion's Science Advisory Panel as supplemental material to the risk assessment manuscript. This will provide the context needed to view these questions. We will provide EPA a copy of the submitted version of the manuscript and supplemental material once it has been submitted to the journal this summer.

4.3 Calculation Details

4.3.1 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 7**.

Table 7. 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 7**, 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 7** can readily be copy and pasted into USEPA's BMDS spreadsheet program for the purposes of rerunning any dose-response models.

4.3.2 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 8**.

Table 8. Dose-Response Data Used to Assess Ovarian Atrophy in Mice and Rats Exposed to BD

		BD Exposure				Response
Species	**Exposure Duration, weeks**	**ppm, as tested (6 hours/day,**	**Step 1: ppm, Continuous**	**Step 2: ppm, Human Equivalent Concentration**	**Step 3: Adjustments to Express Rat Values in Terms of Mouse**	**Incidence Ovarian Atrophy**

	(Reference)	5 days/ week)			Sensitivity (toxicodynamic differences)	
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 8**, 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 **Appendix 1** for mouse and rat data combined, and for mouse data alone. Within this appendix, 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).

4.4 Overview of 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 9** and **10**, 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 11** 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 **Appendix 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).

Table 9. 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 10. 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 11: 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

5. References

Abolaji AO, Adedara IA, Abajingin AO, Fatunmibi OJ, Ladipo EO, Farombi EO. Evidence of oxidative damage and reproductive dysfunction accompanying 4-vinylcyclohexene diepoxide exposure in female Wistar rats. Reprod Toxicol. 2016 Dec;66:10-19. doi: 10.1016/j.reprotox.2016.09.009. Epub 2016 Sep 16. PMID: 27647594.

Albertini RJ, Srám RJ, Vacek PM, Lynch J, Nicklas JA, van Sittert NJ, Boogaard PJ, Henderson RF, Swenberg JA, Tates AD, Ward JB Jr, Wright M, Ammenheuser MM, Binkova B, Blackwell W, de Zwart FA, Krako D, Krone J, Megens H, Musilová P, Rajská G, Ranasinghe A, Rosenblatt JI, Rössner P, Rubes J, Sullivan L, Upton P, Zwinderman AH. Biomarkers in Czech workers exposed to 1,3-butadiene: a transitional epidemiologic study. Res Rep Health Eff Inst. 2003 Jun;(116):1-141; discussion 143-62. PMID: 12931846.

Appt SE, Clarkson TB, Hoyer PB, Kock ND, Goode AK, May MC, Persyn JT, Vail NK, Ethun KF, Chen H, Sen N, Kaplan JR. Experimental induction of reduced ovarian reserve in a nonhuman primate model (Macaca fascicularis). Comp Med. 2010 Oct;60(5):380-8. PMID: 21262124; PMCID: PMC2958207.

ARA. 2022. Alliance for Risk Assessment. Beyond Science and Decisions Workshop XIII. https://tera.org/Alliance%20for%20Risk/WorkshopXIII/Workshop_Final_Report_22.pdf

ATSDR. 2012. Toxicological profile for 1,3-butadiene. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Bevan C, Stadler JC, Elliott GS, Frame SR, Baldwin JK, Leung HW, Moran E, Panepinto AS. Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. Fundam Appl Toxicol. 1996 Jul;32(1):1-10. doi: 10.1006/faat.1996.0101. PMID: 8812199.

Bond JA, Csanády GA, Leavens T, Medinsky MA. Research strategy for assessing target tissue dosimetry of 1,3-butadiene in laboratory animals and humans. IARC Sci Publ. 1993;(127):45-55. PMID: 8070886.

Boobis AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, Schlatter J, Seed J, Vickers C. IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit Rev Toxicol. 2008;38(2):87-96. doi: 10.1080/10408440701749421. PMID: 18259981.

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

Boysen G, Rusyn I, Chiu WA, Wright FA. Characterization of population variability of 1,3-butadiene derived protein adducts in humans and mice. Regul Toxicol Pharmacol. 2022 Jul;132:105171. doi: 10.1016/j.yrtph.2022.105171. Epub 2022 Apr 22. PMID: 35469930; PMCID: PMC9575152.

Chi L, Nixon E, Spencer F. Uterine-ovarian biochemical and developmental interactions to the postimplantation treatment with a butadiene metabolite, diepoxybutane, in pregnant rats. J Biochem Mol Toxicol. 2002;16(4):147-53. doi: 10.1002/jbt.10021. PMID: 12242682.

Clerici LA, Cocco B, Sacco MG, Monteggia E, Collotta A. The use of pre-implantation mouse embryos cultured in vitro in toxicological studies. Toxicol In Vitro. 1995 Oct;9(5):577-81. doi: 10.1016/0887-2333(95)00075-j. PMID: 20650132.

Cochrane JE, Skopek TR. Mutagenicity of 1,3-butadiene and its epoxide metabolites in human TK6 cells and in splenic T cells isolated from exposed B6C3F1 mice. IARC Sci Publ. 1993;(127):195-204. PMID: 8070866.

Csanády GA, Guengerich FP, Bond JA. Comparison of the biotransformation of 1,3-butadiene and its metabolite, butadiene monoepoxide, by hepatic and pulmonary tissues from humans, rats and mice. Carcinogenesis. 1992 Jul;13(7):1143-53. doi: 10.1093/carcin/13.7.1143. Erratum in: Carcinogenesis 1993 Apr;14(4):784. PMID: 1638680.

Cui JY, Renaud HJ, Klaassen CD. Ontogeny of novel cytochrome P450 gene isoforms during postnatal liver maturation in mice. Drug Metab Dispos. 2012 Jun;40(6):1226-37. doi: 10.1124/dmd.111.042697. Epub 2012 Mar 23. PMID: 22446519; PMCID: PMC3362787.

Delzell E., N. Sathiakumar, M. Macaluso, M. Hovinga, R. Larson, F. Barbone, C. Beall, P. Cole, J. Julian, D.C.F. Muir, A Follow-Up Study of Synthetic Rubber Workers. Submitted to the International Institute of Synthetic Rubber Producers, 1995. October 2, 1995.

Doerr JK, Hollis EA, Sipes IG. Species difference in the ovarian toxicity of 1,3-butadiene epoxides in B6C3F1 mice and Sprague-Dawley rats. Toxicology. 1996 Oct 28;113(1-3):128-36. doi: 10.1016/0300-483x(96)03437-3. PMID: 8901892.

Doerr JK, Hooser SB, Smith BJ, Sipes IG. Ovarian toxicity of 4-vinylcyclohexene and related olefins in B6C3F1 mice: role of diepoxides. Chem Res Toxicol. 1995 Oct-Nov;8(7):963-9. doi: 10.1021/tx00049a010. PMID: 8555412.

Elfarra, Adnan A., and Xin-Yu Zhang. "Alcohol Dehydrogenase- and Rat Liver Cytosol-Dependent Bioactivation Of 1-chloro-2-hydroxy-3-butene to 1-chloro-3-buten-2-one, a bifunctional alkylating agent." Chemical Research in Toxicology 25, no. 11 (November 19, 2012): 2600–2607.

Erber L, Goodman S, Wright FA, Chiu WA, Tretyakova NY, Rusyn I. Intra- and Inter-Species Variability in Urinary N7-(1-Hydroxy-3-buten-2-yl)guanine Adducts Following Inhalation Exposure to 1,3-Butadiene. Chem Res Toxicol. 2021 Nov 15;34(11):2375-2383. doi: 10.1021/acs.chemrestox.1c00291. Epub 2021 Nov 2. PMID: 34726909; PMCID: PMC8715497.

Erexson GL, Tindall KR. Micronuclei and gene mutations in transgenic big Blue((R)) mouse and rat fibroblasts after exposure to the epoxide metabolites of 1, 3-butadiene. Mutat Res. 2000 Dec 20;472(1-2):105-17. doi: 10.1016/s1383-5718(00)00136-4. PMID: 11113703.

Filser JG, Faller TH, Bhowmik S, Schuster A, Kessler W, Pütz C, Csanády GA. First-pass metabolism of 1,3-butadiene in once-through perfused livers of rats and mice. Chem Biol Interact. 2001 Jun 1;135-136:249-65. doi: 10.1016/s0009-2797(01)00194-6. PMID: 11397395.

Filser, Johannes G., Swati Bhowmik, Thomas H. Faller, Christoph Hutzler, Winfried Kessler, Supatta Midpanon, Christian Pütz, et al. "Quantitative Investigation on the Metabolism of 1,3-Butadiene and of Its Oxidized Metabolites in Once-through Perfused Livers of Mice and Rats." Toxicological Sciences : An Official Journal of the Society of Toxicology 114, no. 1 (March 2010): 25–37. https://doi.org/10.1093/toxsci/kfp297.

Filser, Johannes Georg, Christoph Hutzler, Veronika Meischner, Vimal Veereshwarayya, and György András Csanády. "Metabolism of 1,3-Butadiene to Toxicologically Relevant Metabolites in Single-Exposed Mice and Rats." Chemico-Biological Interactions 166, no. 1–3 (March 20, 2007): 93–103. https://doi.org/10.1016/j.cbi.2006.03.002.

Fred, C., Törnqvist, M., Granath, F., 2008. Evaluation of Cancer Tests of 1,3-Butadiene Using Internal Dose, Genotoxic Potency, and a Multiplicative Risk Model. Cancer Research 68, 8014-8021.

Fustinoni S, Soleo L, Warholm M, et al. Influence of metabolic genotypes on biomarkers of exposure to 1,3-butadiene in humans. Cancer Epidemiol Biomarkers Prev. 2002;11(10 Pt 1):1082-1090.

Georgieva NI, Boysen G, Bordeerat N, Walker VE, Swenberg JA. 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. 2010 Jun;115(2):322-9. doi: 10.1093/toxsci/kfq060. Epub 2010 Feb 22. PMID: 20176624; PMCID: PMC2871755.

Green JW. 2003. Statistical Analysis of Butadiene Mouse Data from Hackett et al. (1987). Haskell Laboratory for Health and Environmental Sciences, E.I. Dupont de Nemours & Co., Newark, DE, USA: 151 pp.

Hackett, P. L., M. R. Sikov, T. J. Mast, M. G. Brown, R. L. Buschbom, M. L. Clark, J. R. Decker, J. J. Evanoff, R. L. Rommereim and S. E. Rowe (1987a). Inhalation developmental toxicology studies: teratology study of 1,3-butadiene in mice: final report, Pac. Northwest Lab.,Richland,WA,USA.: 92 pp.

Hackett, P. L., M. R. Sikov, T. J. Mast, M. G. Brown, R. L. Buschbom, M. L. Clark, J. R. Decker, J. J. Evanoff, R. L. Rommereim, S. E. Rowe and R.B. Westerberg (1987b). Inhalation developmental toxicology studies of 1,3-butadiene in the rat: final report, Pac. Northwest Lab.,Richland,WA,USA.: 22 pp.

Hart SN, Cui Y, Klaassen CD, Zhong XB. Three patterns of cytochrome P450 gene expression during liver maturation in mice. Drug Metab Dispos. 2009 Jan;37(1):116-21. doi: 10.1124/dmd.108.023812. Epub 2008 Oct 9. PMID: 18845660; PMCID: PMC2683655.

Health Canada. 2000. Priority Substances List Assessment Report. ISBN 0-662-29014-3. Cat. no. En40-215/52E

Himmelstein MW, Asgharian B, Bond JA. High concentrations of butadiene epoxides in livers and lungs of mice compared to rats exposed to 1,3-butadiene. Toxicol Appl Pharmacol. 1995 Jun;132(2):281-8. doi: 10.1006/taap.1995.1109. PMID: 7785055.

Hoyer PB, Sipes IG. Development of an animal model for ovotoxicity using 4-vinylcyclohexene: a case study. Birth Defects Res B Dev Reprod Toxicol. 2007 Apr;80(2):113-25. doi: 10.1002/bdrb.20103. PMID: 17342769.

Irons RD, Pyatt DW, Stillman WS, Som DB, Claffey DJ, Ruth JA. Comparative toxicity of known and putative metabolites of 1, 3-butadiene in human CD34(+) bone marrow cells. Toxicology. 2000 Sep 7;150(1-3):99-106. doi: 10.1016/s0300-483x(00)00249-3. PMID: 10996666.

Kappeler CJ, Hoyer PB. 4-vinylcyclohexene diepoxide: a model chemical for ovotoxicity. Syst Biol Reprod Med. 2012 Feb;58(1):57-62. doi: 10.3109/19396368.2011.648820. PMID: 22239082; PMCID: PMC3307534.

Keller DA, Carpenter SC, Cagen SZ, Reitman FA. In vitro metabolism of 4-vinylcyclohexene in rat and mouse liver, lung, and ovary. Toxicol Appl Pharmacol. 1997 May;144(1):36-44. doi: 10.1006/taap.1996.8098. PMID: 9169067.

Kirman CR, Hays SM. Use of Biomarker Data and Relative Potencies of Mutagenic Metabolites to Support Derivation of Cancer Unit Risk Values for 1,3-Butadiene from Rodent Tumor Data. Toxics. 2022 Jul 15;10(7):394. doi: 10.3390/toxics10070394. PMID: 35878299; PMCID: PMC9316621.

Kirman CR, North CM, Tretyakova NY, Erraguntla N, Shen H, Hays SM. Use of biomarker data and metabolite relative potencies to support derivation of noncancer reference values based on the reproductive and developmental toxicity effects of 1,3-butadiene. Regul Toxicol Pharmacol. 2022 Oct;134:105239. doi: 10.1016/j.yrtph.2022.105239. Epub 2022 Aug 1. PMID: 35926658.

Krause RJ, Elfarra AA. Oxidation of butadiene monoxide to meso- and (+/-)-diepoxybutane by cDNA-expressed human cytochrome P450s and by mouse, rat, and human liver microsomes: evidence for preferential hydration of meso-diepoxybutane in rat and human liver microsomes. Arch Biochem Biophys. 1997 Jan 15;337(2):176-84. doi: 10.1006/abbi.1996.9781. PMID: 9016811.

Kreuzer PE, Kessler W, Welter HF, Baur C, Filser JG. Enzyme specific kinetics of 1,2-epoxybutene-3 in microsomes and cytosol from livers of mouse, rat, and man. Arch Toxicol. 1991;65(1):59-67. doi: 10.1007/BF01973504. PMID: 2043052.

Li J, Fan S, Han D, Xie J, Kuang H, Ge P. Microarray gene expression profiling and bioinformatics analysis of premature ovarian failure in a rat model. Exp Mol Pathol. 2014 Dec;97(3):535-41. doi: 10.1016/j.yexmp.2014.10.015. Epub 2014 Nov 4. PMID: 25445499.

Li Y, Li M, Liu J, Nie G, Yang H. Altered m6A modification is involved YAP-mediated apoptosis response in 4-vinylcyclohexene diepoxide induced ovotoxicity. Ecotoxicol Environ Saf. 2023 Jun 30;262:115192. doi: 10.1016/j.ecoenv.2023.115192. Epub ahead of print. PMID: 37393819.

Liu W, Wang LY, Xing XX, Fan GW. Conditions and possible mechanisms of VCD-induced ovarian failure. Altern Lab Anim. 2015 Dec;43(6):385-92. doi: 10.1177/026119291504300606. PMID: 26753941.

Marty MS, Erraguntla N, North C, Barranco WT, Kirman CR, Cagen S, Rushton EK, Shen H, Koehler MW, Budinsky R. A reproductive and developmental toxicity screening study of 1,3-butadiene in Sprague-Dawley rats. Regul Toxicol Pharmacol. 2021 Dec;127:105066. doi: 10.1016/j.yrtph.2021.105066. Epub 2021 Oct 23. PMID: 34699959.

Meek ME, Palermo CM, Bachman AN, North CM, Jeffrey Lewis R. Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence. J Appl Toxicol. 2014 Jun;34(6):595-606. doi: 10.1002/jat.2984. Epub 2014 Feb 10. PMID: 24777878; PMCID: PMC4321063.

Meng RQ, Hackfeld LC, Hedge RP, Wisse LA, Redetzke DL, Walker VE; HEI Health Review Committee. Mutagenicity of stereochemical configurations of 1,3-butadiene epoxy metabolites in human cells. Res Rep Health Eff Inst. 2010 Jun;(150):1-34; discussion 35-41. PMID: 20853577.

Motwani, Hitesh V., and Margareta Törnqvist. "In Vivo Doses of Butadiene Epoxides as Estimated from in Vitro Enzyme Kinetics by Using Cob(I)Alamin and Measured Hemoglobin Adducts: An Inter-Species Extrapolation Approach." Toxicology and Applied Pharmacology 281, no. 3 (December 15, 2014): 276–84. https://doi.org/10.1016/j.taap.2014.10.011.

Nakamura J, Carro S, Gold A, Zhang Z. An unexpected butadiene diolepoxide-mediated genotoxicity implies alternative mechanism for 1,3-butadiene carcinogenicity. Chemosphere. 2021 Mar;266:129149. doi: 10.1016/j.chemosphere.2020.129149. Epub 2020 Nov 30. PMID: 33310515.

NTP, 1984. Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). N. T. Program, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health.

NTP, 1993. NTP Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser 434: 1-389.

OEHHA. 2013. 1,3-Butadiene Reference Exposure Levels.

Owen PE, Glaister JR, Gaunt IF, Pullinger DH. Inhalation toxicity studies with 1,3-butadiene. 3. Two year toxicity/carcinogenicity study in rats. Am Ind Hyg Assoc J. 1987 May;48(5):407-13. doi: 10.1080/15298668791384959. PMID: 3591659.

Sathiakumar N. and Delzell, E. 2009. A follow-up study of mortality among women in the North American Synthetic Rubber Industry. J Occup Environ Med.51:1314-1325.

Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., and Delzell, E. 2021a. 1,3-Butadiene, styrene and lymphohaematopoietic cancers among North American synthetic rubber polymer workers: exposure-response analyses, Occup. Environ. Med. 78(12), 859-868. doi: 10.1136/oemed-2020-107197

Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., and Delzell, E. 2021b. 1,3-Butadiene, Styrene and Selected Outcomes Among Synthetic Rubber Polymer workers: Updated Exposure-Response Analyses. Chemico-Biological Interactions. 109600. PMID 34324853 DOI: 10.1016/j.cbi.2021.109600

Sathiakumar, N., Graff, J., Macaluso, M., Maldonado, G., Matthews, R., and Delzell, E. 2005. An Updated Study of Mortality Among North American Synthetic Rubber Industry Workers. Occup Environ Med. 62:822-829.

Sathiakumar, N., Tipre, M., Leader, M., Brill, I., and Delzell, E. 2019. Mortality Among Men and Women in the North American Synthetic Rubber Industry, 1943 to 2009, J. Occup. Environ. Med. 61 (2019) 887-897. doi:10.1097/JOM.0000000000001688

Schmidt U, Loeser E. Species differences in the formation of butadiene monoxide from 1,3-butadiene. Arch Toxicol. 1985 Sep;57(4):222-5. doi: 10.1007/BF00324781. PMID: 3879165.

Seaton MJ, Follansbee MH, Bond JA. Oxidation of 1,2-epoxy-3-butene to 1,2:3,4-diepoxybutane by cDNA-expressed human cytochromes P450 2E1 and 3A4 and human, mouse and rat liver microsomes. Carcinogenesis. 1995 Oct;16(10):2287-93. doi: 10.1093/carcin/16.10.2287. PMID: 7586124.

Sen Halicioglu B, Saadat KASM, Tuglu MI. The relationship of 4-vinylcyclohexene diepoxide toxicity with cell death, oxidative stress, and gap junctions in female rat ovaries. Reprod Med Biol. 2021 Jun 22;20(4):543-553. doi: 10.1002/rmb2.12398. PMID: 34646083; PMCID: PMC8499605.

Song W, Qiu YT, Li XZ, Sun QY, Chen LN. 4-vinylcyclohexene diepoxide induces apoptosis by excessive reactive oxygen species and DNA damage in human ovarian granulosa cells. Toxicol In Vitro. 2023 Sep;91:105613. doi: 10.1016/j.tiv.2023.105613. Epub 2023 May 12. PMID: 37182589.

Springer LN, Tilly JL, Sipes IG, Hoyer PB. Enhanced expression of bax in small preantral follicles during 4-vinylcyclohexene diepoxide-induced ovotoxicity in the rat. Toxicol Appl Pharmacol. 1996 Aug;139(2):402-10. doi: 10.1006/taap.1996.0181. PMID: 8806858.

Swenberg JA, Bordeerat NK, Boysen G, et al. 1,3-Butadiene: Biomarkers and application to risk assessment. Chem Biol Interact. 2011;192(1-2):150-154. doi:10.1016/j.cbi.2010.10.010

Swenberg JA, Boysen G, Georgieva N, Bird MG, Lewis RJ. Future directions in butadiene risk assessment and the role of cross-species internal dosimetry. Chem Biol Interact. 2007 Mar 20;166(1-3):78-83. doi: 10.1016/j.cbi.2007.01.012. Epub 2007 Feb 3. PMID: 17343837.

TCEQ, 2015. Development Support Document. 1,3-Butadiene CAS Registry Number: 106-99-0. Final, August 7, 2008; Accessible 2013; 24-Hour Reference Value added, September 14, 2015.

Thornton-Manning JR, Dahl AR, Allen ML, Bechtold WE, Griffith WC Jr, Henderson RF. Disposition of butadiene epoxides in Sprague-Dawley rats following exposures to 8000 ppm 1,3-butadiene: comparisons with tissue epoxide concentrations following low-level exposures. Toxicol Sci. 1998 Feb;41(2):167-73. doi: 10.1006/toxs.1997.2403. PMID: 9520352.

Thornton-Manning JR, Dahl AR, Bechtold WE, Griffith WC Jr, Henderson RF. 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. 1995b Aug;16(8):1723-31. doi: 10.1093/carcin/16.8.1723. PMID: 7634396.

Thornton-Manning JR, Dahl AR, Bechtold WE, Griffith WC Jr, Henderson RF. Comparison of the disposition of butadiene epoxides in Sprague-Dawley rats and B6C3F1 mice following a single and repeated exposures to 1,3-butadiene via inhalation. Toxicology. 1997 Nov 21;123(1-2):125-34. doi: 10.1016/s0300-483x(97)00112-1. PMID: 9347927.

USEPA. 2002. Health Assessment of 1,3-Butadiene. U.S. Environmental Protection Agency. EPA/600/P-98/001F

USEPA. 2014. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. U.S. Environmental Protection Agency. EPA/R-14/002F.

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;188(3):668-676. doi:10.1016/j.cbi.2010.06.017

Valdez-Flores C, Erraguntla N, Budinsky R, Cagen S, Kirman CR. An updated lymphohematopoietic and bladder cancers risk evaluation for occupational and environmental exposures to 1,3-butadiene. Chem Biol Interact. 2022 Oct 1;366:110077. doi: 10.1016/j.cbi.2022.110077. Epub 2022 Aug 25. Erratum in: Chem Biol Interact. 2023 Nov 1;385:110736. PMID: 36029806.

Wang, Ye, Ying-Xin Yu, Yang Luan, Jing An, Dong-Guang Yin, and Xin-Yu Zhang. “Bioactivation of 1-Chloro-2-Hydroxy-3-Butene, an in Vitro Metabolite of 1,3-Butadiene, by Rat Liver Microsomes.” Chemico-Biological Interactions 282 (February 25, 2018): 36–44. https://doi.org/10.1016/j.cbi.2018.01.006.

Wu, Wen-Jing, Wei-Feng Tang, Ming-Hui Xiang, Jianshe Yan, Xiumei Cao, Chang-Hui Zhou, Yan Chang, et al. “Isotope Dilution LC/ESI(-)-MS-MS Quantitation of Urinary 1,4-Bis(N-Acetyl-S-Cysteinyl)-2-Butanone in Mice and Rats as the Biomarker Of 1-chloro-2-hydroxy-3-butene, an in vitro metabolite of 1,3-butadiene.” Chemico-Biological Interactions 311 (September 25, 2019): 108760. https://doi.org/10.1016/j.cbi.2019.108760.

Zhou Q, Jin X, Wang J, Li H, Yang L, Wu W, Chen W. 4-vinylcyclohexene diepoxide induces premature ovarian insufficiency in rats by triggering the autophagy of granule cells through regulating miR-144. J Reprod Immunol. 2023 Jun;157:103928. doi: 10.1016/j.jri.2023.103928. Epub 2023 Mar 5. PMID: 36889083.

Appendices

Appendix 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
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
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
1283	C	65
1283	C	67
1283	C	75
1283	C	75
1283	C	77
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
1283	I	105
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
1283	C	105
1283	C	105
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
1283	C	106
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
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	C	105
4105	C	105
4105	C	105
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	I	56
12828	I	56
12828	C	59
12828	C	60
12828	I	65
12828	I	65
12828	I	65
12828	I	65
12828	I	65
12828	I	65

12828	I	65
12828	I	65
12828	I	65
12828	C	65
12828	I	75
12828	I	76
12828	I	77
12828	I	78
12828	I	78
12828	I	82
12828	I	82
12828	I	83
12828	I	84
12828	I	85
12828	I	86
12828	I	87
12828	I	88
12828	I	90
12828	I	90
12828	I	92
12828	I	93
12828	C	93
12828	C	93
12828	I	94
12828	I	94
12828	C	94
12828	I	95
12828	C	95
12828	I	96
12828	I	98
12828	I	100
12828	C	100
12828	I	101
12828	I	104
12828	C	104
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105

12828	I	105
12828	C	105
41051	C	2
41051	C	30
41051	I	39
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	C	40
41051	I	46
41051	I	49
41051	I	50
41051	I	51
41051	I	53
41051	I	53
41051	I	54
41051	I	56
41051	C	57
41051	I	59
41051	I	59
41051	I	60
41051	I	63
41051	I	64
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	C	65
41051	C	65
41051	C	65
41051	C	65
41051	I	66
41051	I	67
41051	I	67

41051	I	68
41051	I	68
41051	I	68
41051	I	69
41051	I	70
41051	I	70
41051	I	70
41051	I	70
41051	I	72
41051	I	72
41051	I	73
41051	I	73
41051	I	74
41051	I	75
41051	I	76
41051	I	78
41051	I	82
41051	I	82
41051	I	82
41051	I	82
41051	C	82
41051	I	86
41051	C	86
41051	I	90
41051	I	90
41051	I	95
41051	I	100
41051	C	101
128284	C	2
128284	I	29
128284	I	30
128284	I	32
128284	I	32
128284	I	33
128284	I	33
128284	I	34
128284	C	35
128284	C	36
128284	I	37
128284	I	37
128284	I	37
128284	I	37
128284	I	39
128284	I	40

128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	C	40
128284	I	41
128284	I	41
128284	I	41
128284	I	41
128284	I	41
128284	C	41
128284	C	41
128284	I	42
128284	I	42
128284	I	43
128284	I	43
128284	I	43
128284	I	43
128284	I	44
128284	C	44
128284	I	45
128284	I	45
128284	I	46
128284	I	46
128284	I	46
128284	I	46
128284	I	46
128284	C	46
128284	I	47
128284	I	47
128284	C	47
128284	C	47
128284	I	48
128284	I	48
128284	I	48
128284	I	48
128284	I	49
128284	I	50
128284	I	51
128284	I	51

128284	I	51
128284	I	52
128284	I	53
128284	I	53
128284	I	53
128284	I	53
128284	I	54
128284	I	54
128284	I	54
128284	I	55
128284	I	55
128284	I	55
128284	I	55
128284	I	56
128284	I	56
128284	I	56
128284	I	57
128284	I	57
128284	I	58
128284	I	60
128284	I	60
128284	I	60
128284	I	61
128284	I	61
128284	I	63
128284	I	64
128284	I	65
128284	I	65
128284	I	65
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61

0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61

128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
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
0	C	13
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
205255	C	13
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104

0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104

0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
0	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104

970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104

970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104

970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
970	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104

7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104

7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
7760	C	104
0	C	13
0	C	13
0	C	13
0	C	13
0	C	13
0	C	13
0	C	13
0	C	13
0	C	13
0	C	13
970	C	13
970	C	13
970	C	13

970	C	13
970	C	13
970	C	13
970	C	13
970	C	13
970	C	13
970	C	13
0	C	5
0	C	6
0	C	8
0	C	9
0	C	9
0	C	9
0	C	9
0	C	9
0	C	9
0	C	9
0	C	10
0	C	10
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
291	C	9
1455	C	7
1455	C	7
1455	C	9
1455	C	9
1455	C	9
1455	C	9
1455	C	9
1455	C	9
1455	C	9
1455	C	9
1455	C	9
1455	C	9
1455	C	9

5820	C	6
5820	C	9
5820	C	9
5820	C	9
5820	C	9
5820	C	9
5820	C	9
5820	C	9
5820	C	9
5820	C	9
5820	C	9
5820	C	9

A1.2 Mouse Data Alone (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
515
-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
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
0	C	106
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
1283	C	65
1283	C	67
1283	C	75
1283	C	75
1283	C	77
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
1283	I	105
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
1283	C	105
1283	C	105
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

1283	C	106
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
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	I	105
4105	C	105
4105	C	105
4105	C	105
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	C	40
12828	I	56
12828	I	56
12828	C	59
12828	C	60
12828	I	65
12828	I	65
12828	I	65
12828	I	65
12828	I	65
12828	I	65
12828	I	65
12828	I	65

12828	I	65
12828	C	65
12828	I	75
12828	I	76
12828	I	77
12828	I	78
12828	I	78
12828	I	82
12828	I	82
12828	I	83
12828	I	84
12828	I	85
12828	I	86
12828	I	87
12828	I	88
12828	I	90
12828	I	90
12828	I	92
12828	I	93
12828	C	93
12828	C	93
12828	I	94
12828	I	94
12828	C	94
12828	I	95
12828	C	95
12828	I	96
12828	I	98
12828	I	100
12828	C	100
12828	I	101
12828	I	104
12828	C	104
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	I	105
12828	C	105

41051	C	2
41051	C	30
41051	I	39
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	I	40
41051	C	40
41051	I	46
41051	I	49
41051	I	50
41051	I	51
41051	I	53
41051	I	53
41051	I	54
41051	I	56
41051	C	57
41051	I	59
41051	I	59
41051	I	60
41051	I	63
41051	I	64
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	I	65
41051	C	65
41051	C	65
41051	C	65
41051	C	65
41051	I	66
41051	I	67
41051	I	67
41051	I	68
41051	I	68

41051	I	68
41051	I	69
41051	I	70
41051	I	70
41051	I	70
41051	I	70
41051	I	72
41051	I	72
41051	I	73
41051	I	73
41051	I	74
41051	I	75
41051	I	76
41051	I	78
41051	I	82
41051	I	82
41051	I	82
41051	I	82
41051	C	82
41051	I	86
41051	C	86
41051	I	90
41051	I	90
41051	I	95
41051	I	100
41051	C	101
128284	C	2
128284	I	29
128284	I	30
128284	I	32
128284	I	32
128284	I	33
128284	I	33
128284	I	34
128284	C	35
128284	C	36
128284	I	37
128284	I	37
128284	I	37
128284	I	37
128284	I	39
128284	I	40
128284	I	40
128284	I	40

128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	I	40
128284	C	40
128284	I	41
128284	I	41
128284	I	41
128284	I	41
128284	I	41
128284	C	41
128284	C	41
128284	I	42
128284	I	42
128284	I	43
128284	I	43
128284	I	43
128284	I	43
128284	I	44
128284	C	44
128284	I	45
128284	I	45
128284	I	46
128284	I	46
128284	I	46
128284	I	46
128284	I	46
128284	C	46
128284	I	47
128284	I	47
128284	C	47
128284	C	47
128284	I	48
128284	I	48
128284	I	48
128284	I	48
128284	I	49
128284	I	50
128284	I	51
128284	I	51
128284	I	51
128284	I	52

128284	I	53
128284	I	53
128284	I	53
128284	I	53
128284	I	54
128284	I	54
128284	I	54
128284	I	55
128284	I	55
128284	I	55
128284	I	55
128284	I	56
128284	I	56
128284	I	56
128284	I	57
128284	I	57
128284	I	58
128284	I	60
128284	I	60
128284	I	60
128284	I	61
128284	I	61
128284	I	63
128284	I	64
128284	I	65
128284	I	65
128284	I	65
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61

0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
0	C	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61

128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
128284	I	61
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
0	C	13
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

Appendix 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;
```

```
   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;
```

```
  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;
```

```
   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;
```

```
  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;
```

```
   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;
```

```
  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;
```

```
   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;
```

```
  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;
```

```
   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

White Paper: Identification of Key Exposure Pathways for 1,3-Butadiene (BD)

Prepared for:
American Chemistry Council
1,3-Butadiene TSCA Risk Evaluation Consortium

Prepared by:

April 18, 2024

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, releases to the environment, historical trends, and identification of important exposure pathways.

1. Chemical-Physical Properties

- Based on physical chemical (PC) properties (high Henry's law, vapor pressure, low-to-insoluble in water; **Table 1**; adapted from USEPA's *Final Scope of the Risk Evaluation for 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 air concentrations, BD can cause asphyxiation by displacement of oxygen in air.
- A separate white paper has been prepared that covers the chemical-physical properties of BD (unpublished white paper: *1,3-Butadiene Overview*).

Table 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

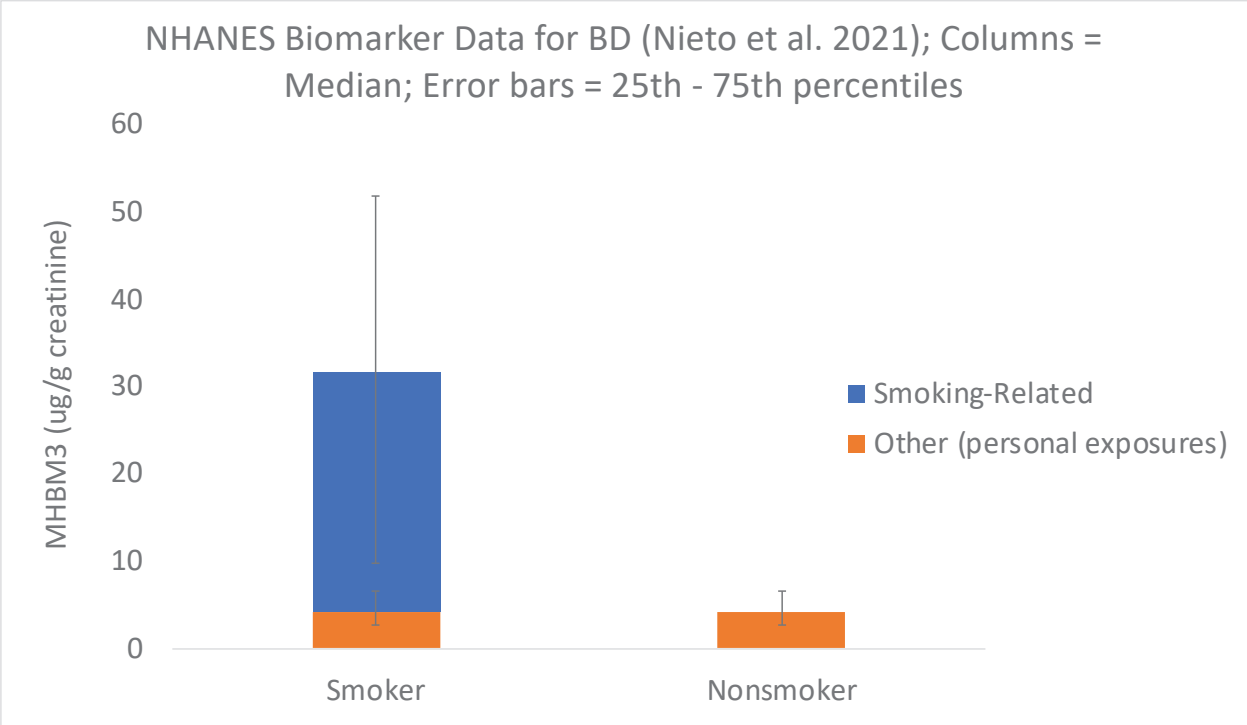
[a] Measured unless otherwise noted.

NA = Not applicable

2. 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**).
- Biomarker measurements in nonsmokers reflect recent personal exposures to BD (e.g., ambient air, indoor air, in-vehicle air, etc.).

Figure 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 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 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).

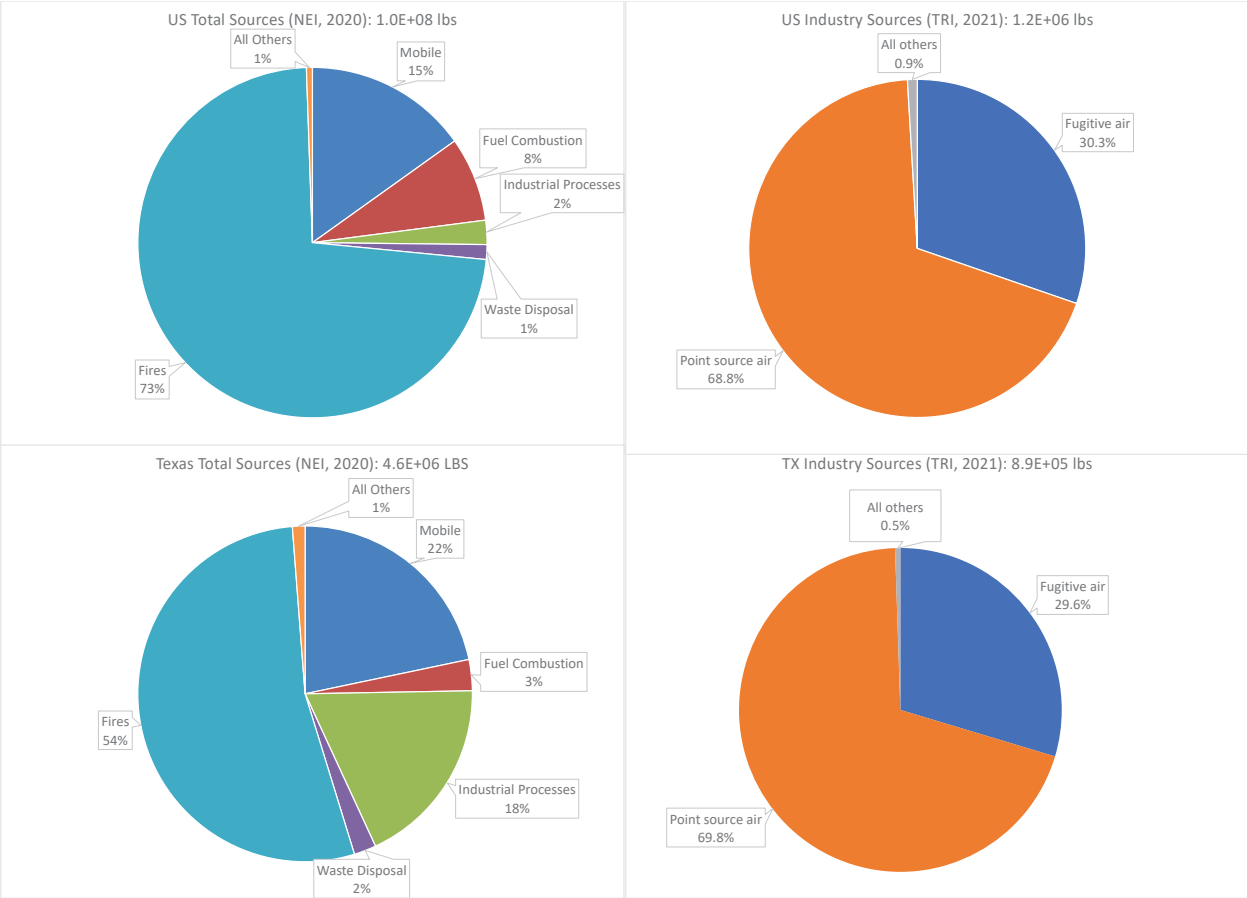
***Assumed constant over time

3. 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**) 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 (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 2**).
        - EPA Toxics Release Inventory database (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 being negligible (<1%) (**Figure 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.

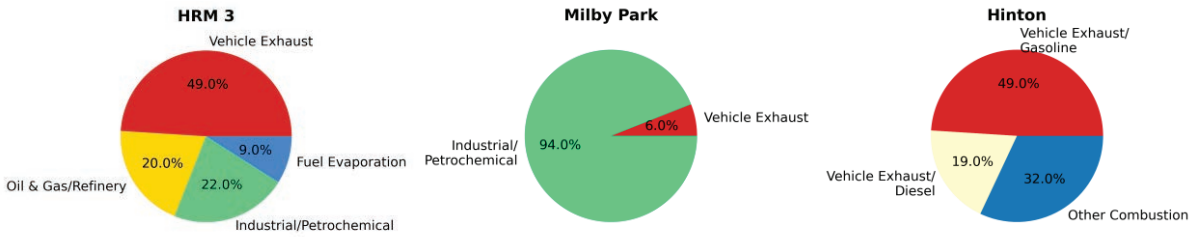
- Texas Data:
  - In Texas, as a state that produces a large portion of BD in the US, NEI (2020) reports that over 4.6E+06 lbs of BD were released, of which fires (54%), mobile sources (22%), and industrial processes and disposal (21% combined) represent the largest sources (**Figure 2**).
  - EPA Toxics 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 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 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**), 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 3**).

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



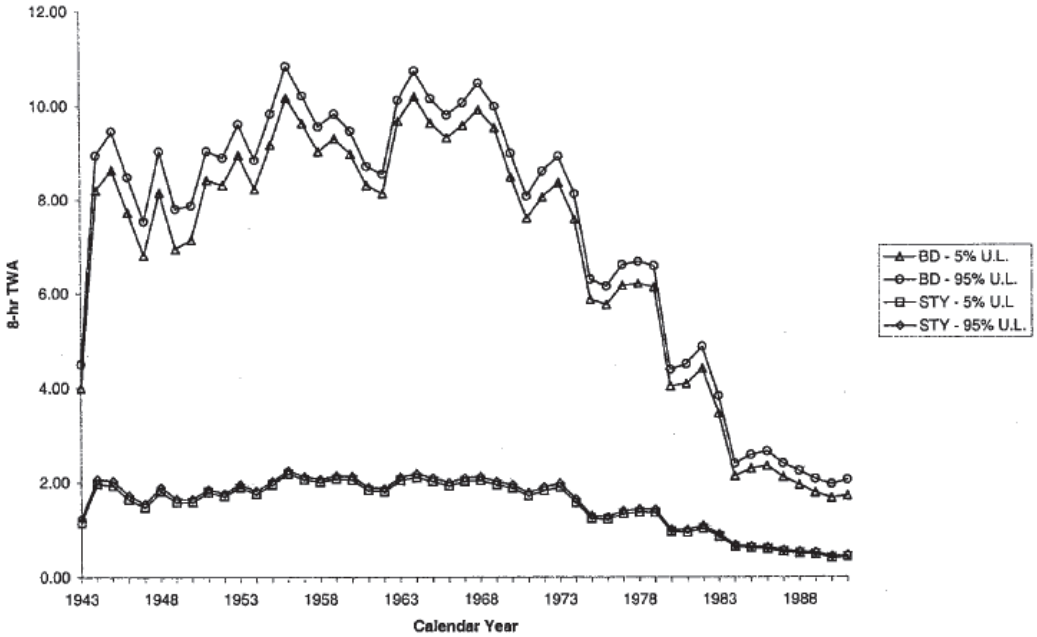
4. Exposures to BD in the U.S. Have Decreased Over Time and are Currently Low

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

4.1 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 4**).

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



- The refined exposure estimates from the Macaluso et al (2004) study, shown in **Figure 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 3;** IISRP, 2020)

Table 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

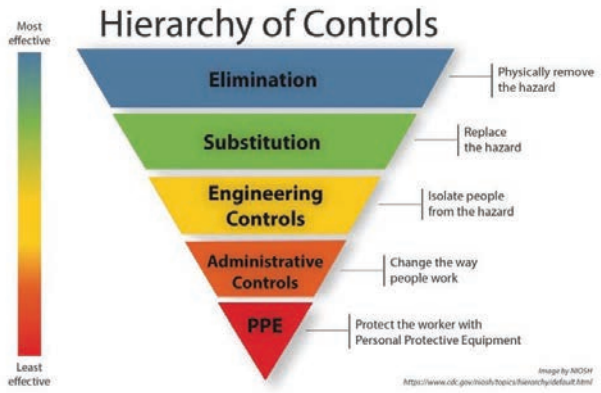
- Similarly, full-shift exposures to BD manufacturing workers are also generally below 0.5 ppm under current routine conditions (**Table 4;** Panko et al. 2023).

Table 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 5**).

Figure 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 5**).

Table 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

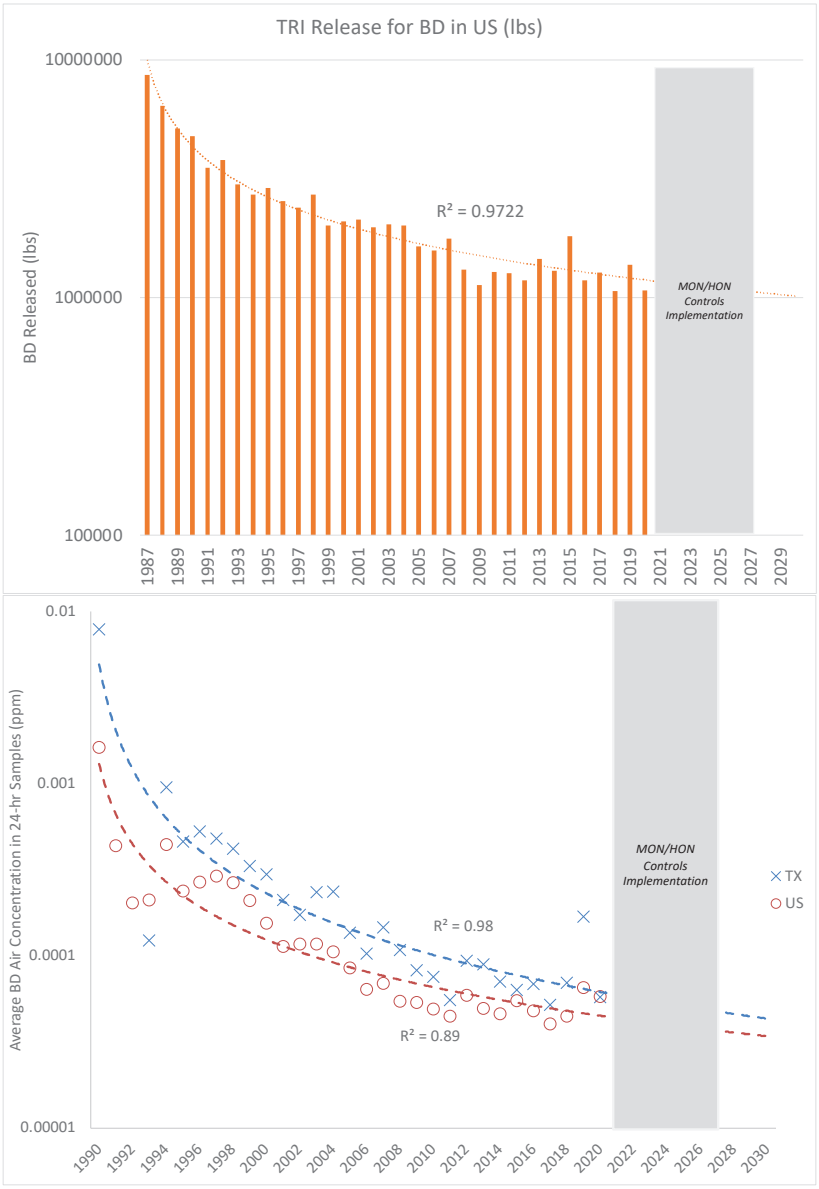
Note: APR = air-purifying respirator.

- 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/m3 (0.054±0.17 ppm).

4.2 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 6A; 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 6B**, EPA AMA, 2020).

Figure 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 air concentrations for two air monitoring locations in Houston, Texas near a BD facility are provided in **Table 6** (AECOM, 2024).

Table 6. Measured Air Concentrations at Two Locations near Houston, Texas (AECOM, 2024)

	BD Annual Average (±SD) Air Concentration (ppm; reflects BD from all sources)	
Monitoring Station	**2019**	**2021**
HRM-3 (far from facility)	0.000080± 0.00032	0.00013± 0.00067
HRM-16 (near facility)	0.00018± 0.0025	0.00023 0.00064

5. 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 95th percentile of 0.00059 ppm, which as noted above reflect BD from a variety of sources.
- 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). 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).

6. 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**) BD is expected to volatilize from water, other media, and from human skin. BD is a gas at standard temperature and pressure, 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 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).

7. 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**), 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 7**). 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 have limited to no bioavailability. 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 7. 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 (⩽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 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 8**); mean values ranging from 0.68-2.14mg/kg for ABS samples (**Tables 9**). Furthermore, the migration/bioavailability of these residuals into simulated food media (solutions of acetic acid, ethanol, or olive oil) is very low (**Table 10**).
- 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 8. Survey Results for Residual BD Monomer in Rubber (conducted in the first Quarter 2020 in the US; IISRP, 2020)

Table 9. Unpublished Data for Residual BD Monomer in ABS Plastics

				Residual BD (mg/kg)			
Year of analysis	**Sample**	**Analytical Method**	**Detection Frequency**	**Minimum**	**Maximum**	**Mean**	**SD**
2001	ABS 1	GCMS	0/1	--	--	<1 mg/kg	--
2001	ABS 2	GCMS	0/1	--	--	<1 mg/kg	--
2001	ABS 3	GCMS	0/1	--	--	<1 mg/kg	--
2001	ABS 4	GCMS	1/1	--	--	1 mg/kg	--
2020-2023	ABS 5*	Not specified	53/56	0.2	3.15	0.68	0.71
2020-2023	ABS 6*	Not specified	595/595	0.1	10.4	2.14	1.47

Overview -1,3-Butadiene Physical and Chemical Properties

Summary

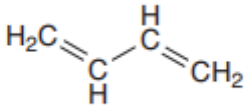
This paper provides a high-level description and overview of 1,3-Butadiene manufacture and use as a reactant. 1,3-Butadiene is generally used in the manufacture of synthetic rubber, or to manufacture other chemicals. It is important to understand its physical and chemical properties, as they are unique compared to other chemicals that have undergone the TSCA Risk Evaluation Process.

Table of Contents

A. What is 1,3-Butadiene?

1,3-Butadiene (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 C_4H_6 and its chemical structure is represented in Figure 1 [1].

Figure 1
1,3-Butadiene



B. What are the physical and chemical properties of 1,3-butadiene?

A summary of physical and chemical properties is shown in Table 1, as compiled by the EPA in the "Final Scope of the Risk Evaluation for 1,3-Butadiene" [2].

1,3-butadiene is a gas at ambient temperature and pressure. It is highly flammable and susceptible to ignition due to its extremely low flash point. It is a liquid below 24^{o} F. Contact with the liquid butadiene can cause frostbite. Its vapors are heavier than air and a flame can flash back to the source of a leak very easily. It can asphyxiate by the displacement of air. [3] It polymerizes readily, especially in the presence of oxygen. [1] With respect to water solubility, it is important to understand that although the experimental water solubility of 1,3-butadiene measured value at 20 ^{o}C was reported as 735 mg/L, the measurement was performed in a closed system. In the NIH *Report on Carcinogens*, it is described as insoluble in water [1].

Table 1 – Physical and Chemical Properties of 1,3-Butadiene

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

C. How is 1,3-Butadiene Made?

1,3-Butadiene is produced commercially by three processes [4]:

- Steam Cracking of Paraffinic Hydrocarbons - Butadiene is a co-product in the manufacture of ethylene (the ethylene co-product process).
- Catalytic Dehydrogenation of n-Butane and n-Butene (the Houdry process*).
- Oxidative Dehydrogenation of n-Butene (the Oxo-D or O-X-D process*).

  * *The Houdry and Oxo-D process descriptions can be found in reference 4 or 5.*

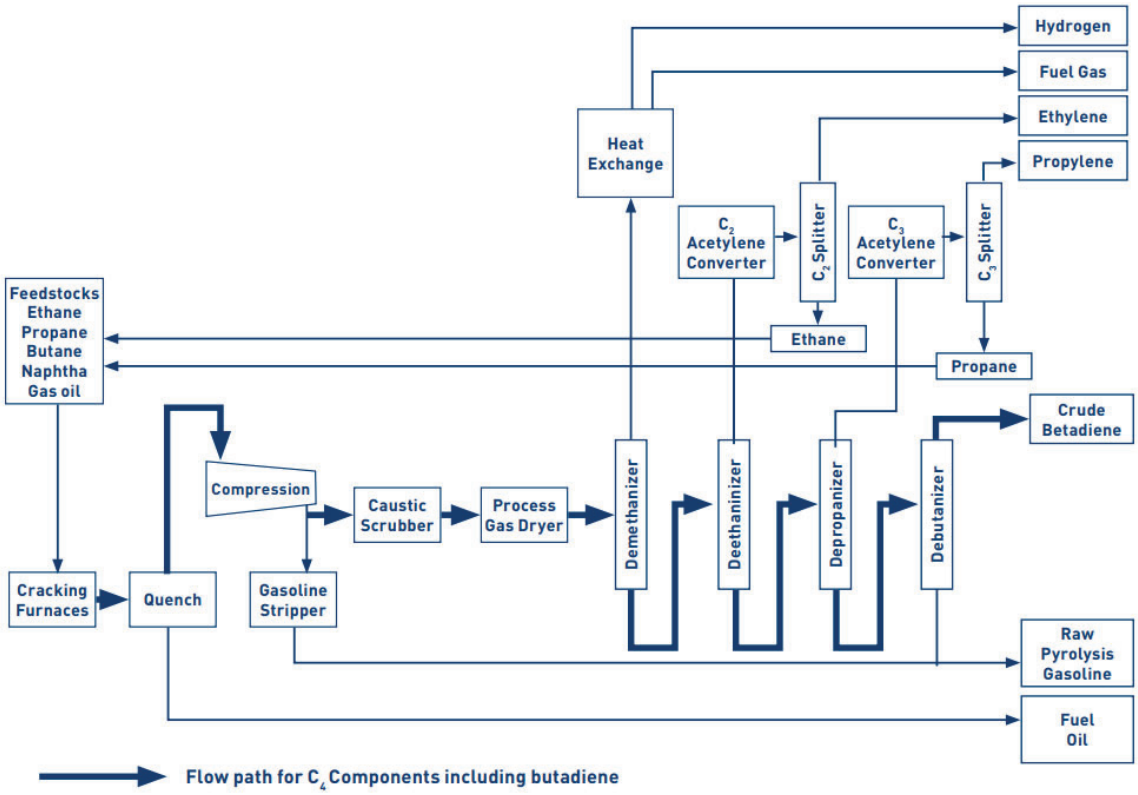
The predominant process is the steam cracking of paraffinic hydrocarbons, accounting for over 96% of global butadiene production in 2022, according to S&P Global Commodity Insights [5].

It is important to note that the processes described below are an enclosed system and any emissions from the system are controlled by pollution control equipment to minimize emissions, as required by EPA Clean Air Act operating permits and state regulations.

Feedstocks, such as ethane, propane, butane, naphtha, or gas oil, are fed in a pyrolysis furnace and combined with steam and heated to temperatures between 1450 and 1525 °F (790-830 °C) to “crack” the hydrocarbon feed molecules. The products made by this process include hydrogen, ethylene, propylene, butadiene, benzene, toluene, and other olefins co-products. After the pyrolysis reaction is quenched, the co-products are separated by distillation. Figure 2 depicts a typical Olefins Plant process flow [4]. Note that this figure does not represent any specific plant process but is provided to give a general overview. The 1,3-butadiene ends up in a stream commonly referred to as crude butadiene, which is a mixture of predominately C4 (hydrocarbons with 4 carbon atoms) that is rich in 1,3-butadiene.

The relative concentration of 1,3-butadiene in the crude butadiene stream is dependent on the initial feedstock that is cracked. Lighter feedstocks such as ethane or propane will yield less 1,3-butadiene than a heavy naphtha feedstock [4].

Figure 2: Typical Olefins Plant Process [5]



Other components present in the mixture vary depending on several factors such as feedstock used, operational conditions of the cracking process, and plant design. Examples of components found in the crude butadiene stream may include but are not limited to: i-butane, n-butane, isomers of butene, i-butylene, and C4 acetylenes among others [5].

D. Recovery of 1,3-butadiene

There are several processing options to further isolate 1,3- butadiene from the crude butadiene stream. This list is not all inclusive and many factors determine which process a butadiene manufacturer may use. The prevalent process options include [5]:

1) Recycle back to the olefins plant cracking furnaces;
2) Hydrogenation followed by recycle cracking;
3) Selective hydrogenation of the butadiene to produce an isobutylene/butene-1 rich stream;
4) Butadiene extractive distillation.

The boiling points of the various components are very close to each other. Extractive distillation using solvent is the most common method used to isolate 1,3-butadiene from other components in the crude butadiene stream. There are several solvent extraction processes in use by manufacturers including [6]:

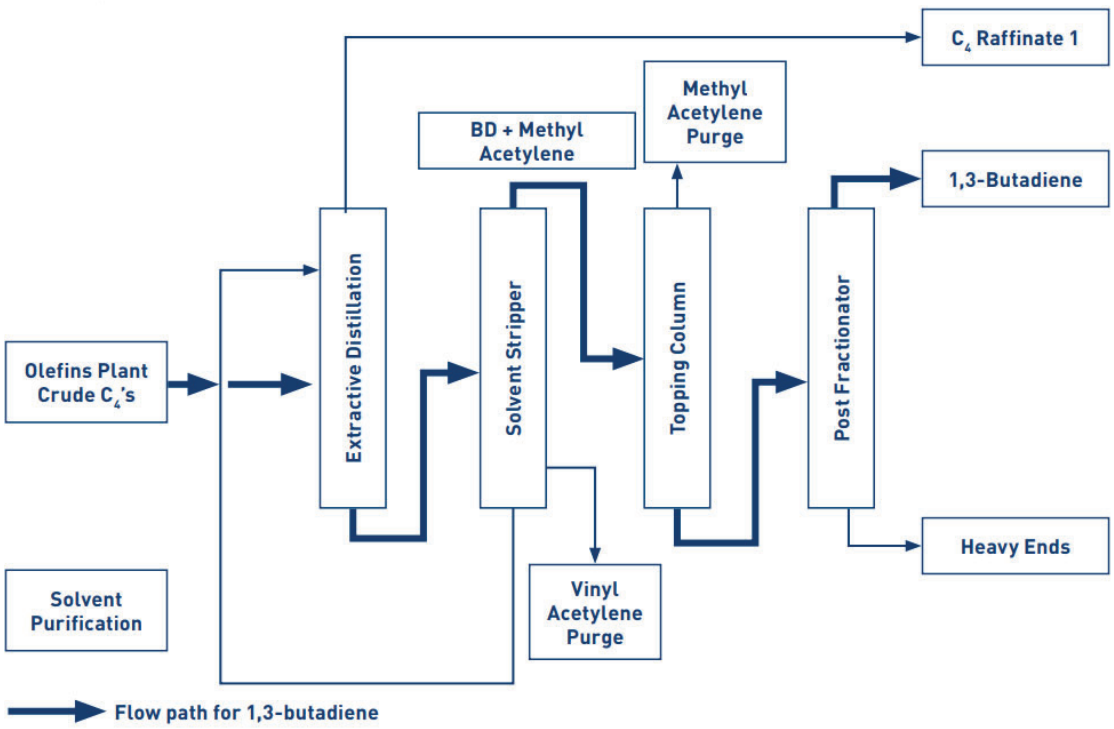
• Acetylene hydrogenation and extractive distillation using aqueous methoxyproprionitrile/furfural;

• extractive/conventional distillation using aqueous n-methyl-2-pyrrolidone;
• dimethylformamide solvent extractive process (nonaqueous); and
• aqueous separation and acetonitrile extraction.

Detailed descriptions of the solvent extraction processes listed above may be found in references [3][4].

Figure 3 shows an example process for extractive distillation process using aqueous separation and acetonitrile. The crude butadiene (C4s) stream is routed to the extractive distillation column. The overheads contain butanes/butylenes (C4 Raffinate 1) and the bottoms consist of 1,3-butadiene and acetylenes. Next, the stream moves to the solvent stripping column, where the solvent is stripped and returned to the initial column while the 1,3-butadiene and methyl acetylene are transported overhead. Vinyl or ethyl acetylene is purged from the stripper bottoms. The topping column is used to separate methyl acetylene while the bottoms from this column can be fed to a post fractionator. The 1,3-butadiene from the overheads is chilled and moved through a coalescer to remove any entrained water. The purity of 1,3-butadiene once this process is complete is typically >99.5% [7].

Figure 3: Example Extractive Distillation Process for 1,3-Butadiene [5]



E. How is 1,3-butadiene stored and transported?

Once the 1,3-butadiene is separated and isolated, it is stored as a liquified or compressed gas in a pressurized sphere, due to its high vapor pressure as required by OSHA standard 1910.110 Hazardous Materials: Storage and handling of liquified petroleum gases [12]. It is important to note that pressurized spheres do not have working losses. Tertiary-butyl catechol (TBC) is added as a stabilizer/inhibitor to prevent peroxide formation [4][5].

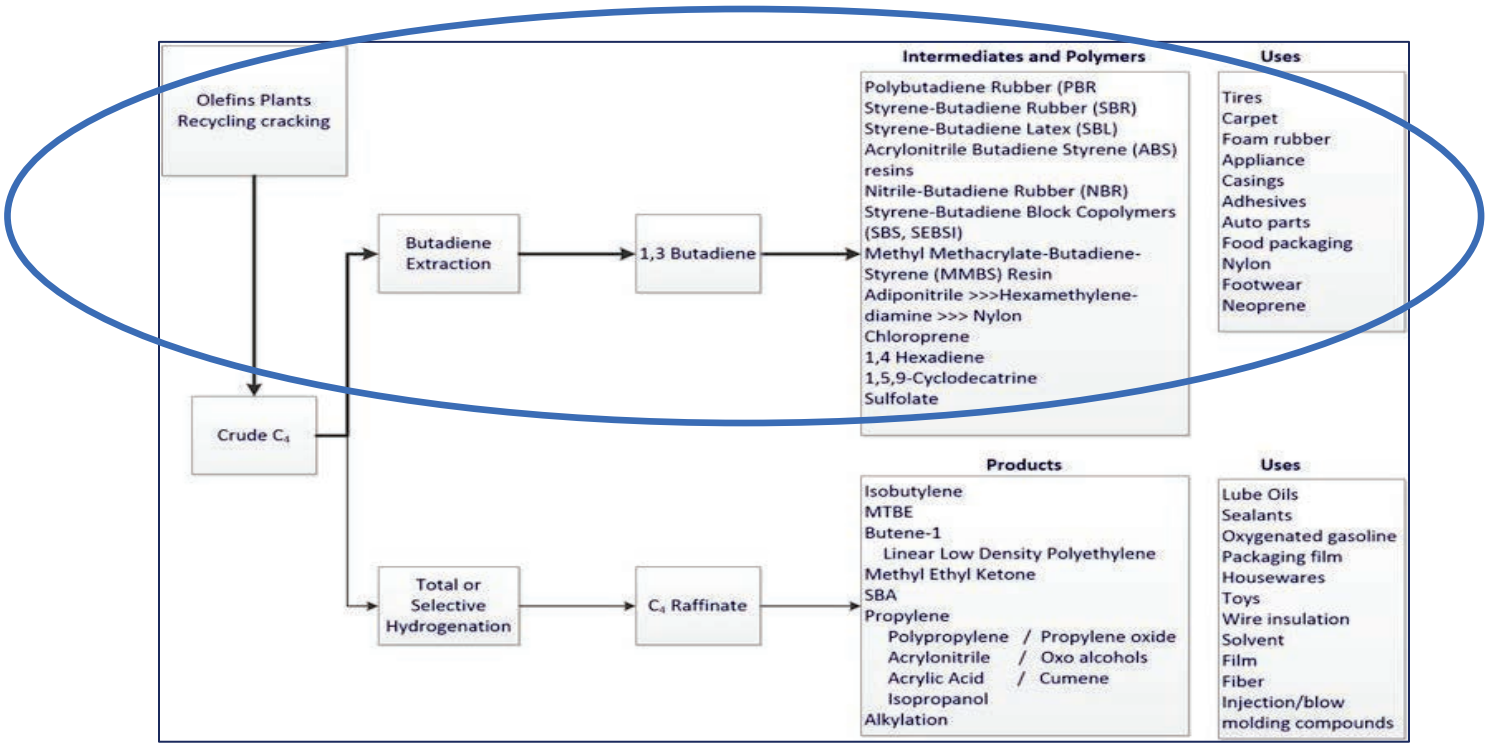
1,3-butadiene with TBC inhibitor is shipped as a liquified product by pipeline, ship, barge, rail tank car and bulk liquid container under pressurized conditions [7]. Transportation is regulated by PHMSA, IMDG and state or local transportation authorities.

F. How is 1,3-butadiene used?

1,3-butadiene 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.

Figure 4 shows an overview of the supply chain for 1,3-butadiene, as modified from the ACC 1,3-Butadiene Product Stewardship Guidance Manual [5]. The upper portion circled shows overall value chain from 1,3-butadiene manufacture to the intermediate chemicals and polymers. End-use products have one or more additional manufacturing steps beyond polymer or intermediate chemical usage before ending up as the consumer good.

Figure 4: Supply Chain Overview of 1,3-Butadiene [5]



G. Description of Chemical/ Polymer Manufacturing using 1,3-Butadiene

Polymerization is the process of chemically bonding monomer building blocks to form large molecules, like individual links attaching together to form a chain. The most basic component of plastic and elastomer materials is polymers [8].

Polybutadiene rubber (PBR) (CAS No. 9003-17-2) is the simplest polymer made from 1,3-butadiene. Other significant use polymers made from 1,3-butadiene include Styrene-Butadiene Rubber (SBR), Styrene-Butadiene Latex (SBL), Nitrile-Butadiene Rubber (NBR), Styrene-Butadiene Block Copolymers (SBS, SEBSI), Methyl Methacrylate-Butadiene Styrene (MMBS) resin and Acrylonitrile Butadiene Styrene resins (ABS). Three dimensional models of many of these polymers may be viewed at the Polymer Science Learning Center website [9].

Manufacture of these polymers is considered a primary condition of use of 1,3-butadiene monomer, as it is consumed in the reaction that creates the polymer. As an example, the general process for the manufacture of Styrene-Butadiene Rubber (SBR) is provided.

1. Styrene Butadiene Copolymer Manufacture Example

Styrene Butadiene Rubber (SBR) or Styrene-Butadiene (SB) latex is composed of the monomer units 1,3-butadiene and styrene. The feed composition and drying process dictates whether the material will be a solid or an emulsion. Generally, if the polymer contains more than 45% 1,3-butadiene (SBR), it will exhibit rubber-like properties. In contrast, the polymer becomes “plastic-like” when the styrene content is over 45% for SB latex [13].

Figure 5 shows the emulsion polymerization process for Styrene-Butadiene Rubber [14]. Monomers of 1,3-butadiene and styrene are fed to a reactor along with a soap solution and activator catalyst modifier. Polymerization is carried out in a series of reactors. The initial product formed in the emulsion phase of the reaction mixture is called latex and is milky white in appearance. Typically, the reaction is stopped when the conversion yield is approximately 60 %, due to decreases in reaction rate and degradation in product quality. This is the reason the “shortstop” is used to stop the reaction at the desired conversion.

Unreacted 1,3-butadiene and styrene monomers in the latex emulsion are recovered and returned to storage for reuse. The latex emulsion is fed to the Flash Tank. Vacuum flashing removes the unreacted butadiene, where it is collected and passed through adsorber/desorber unit and returned to storage for reuse. Next, a steam stripping column is used to recover the styrene from the latex emulsion and returned to the styrene storage tank for reuse. From this point, the latex emulsion moves to storage tank(s).

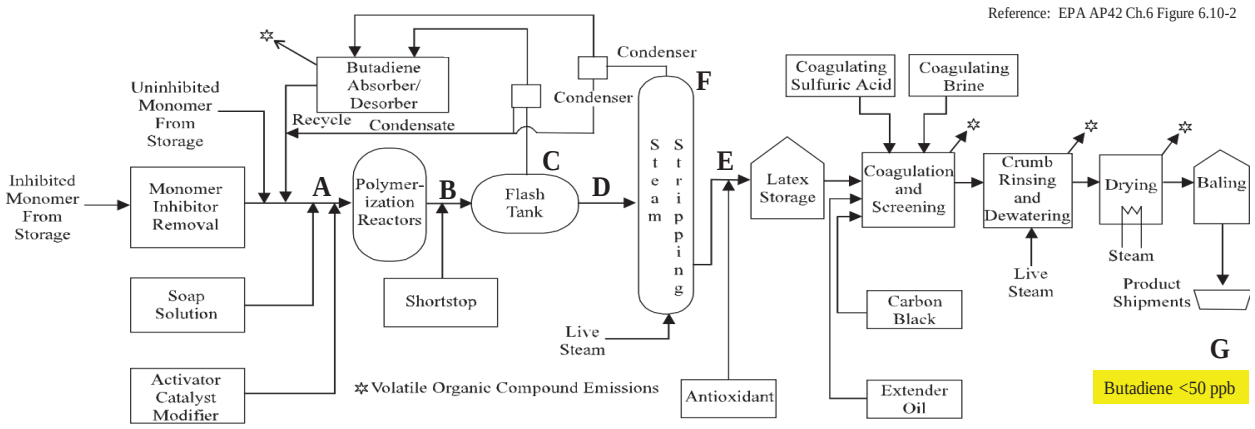
The latex is pumped from the storage tanks to coagulation vessels and receives dilute sulfuric acid and sodium chloride. This brine mixture causes the emulsion to break up and releases the styrene-butadiene polymer as crumb rubber product, followed by rinsing, dewatering, and drying. The polymer crumb rubber is baled and shipped to downstream processors who use it as a material to manufacture their end products. According to information presented in the 1,3-butadiene TSCA risk evaluation docket by

the International Institute of Synthetic Rubber Producers (IISRP) [15], the mass balance residual is less than 50 parts per billion 1,3-butadiene in the crumb SBR product.

Other common types of synthetic rubbers include [16]:

- Acrylonitrile Butadiene Rubbers (NBR)
- Acrylonitrile Butadiene Styrene (ABS)
- Butadiene Rubbers (BR)
- Styrene Isoprene Butadiene Rubbers (SIBR)
- Styrene Block Copolymers (SBC)

Figure 5 - Overview of Emulsion Polymerization process of SBR [14]



Another example of a polymer material made from three components is acetonitrile-butadiene-styrene resin (ABS). Manufacturers use either an aqueous phase reaction process similar to SBR or a continuous mass process, where polybutadiene rubber is dissolved in styrene and acrylonitrile with modifiers and other reaction initiators. The ABS polymer formed from the continuous mass process occurs through phase inversion, where the ABS falls out of solution. The ABS polymer is extruded, cooled in a water bath and chopped into pellets. Since this manufacturing technology begins with polybutadiene, 1,3-butadiene emissions are not expected when this process is used [13].

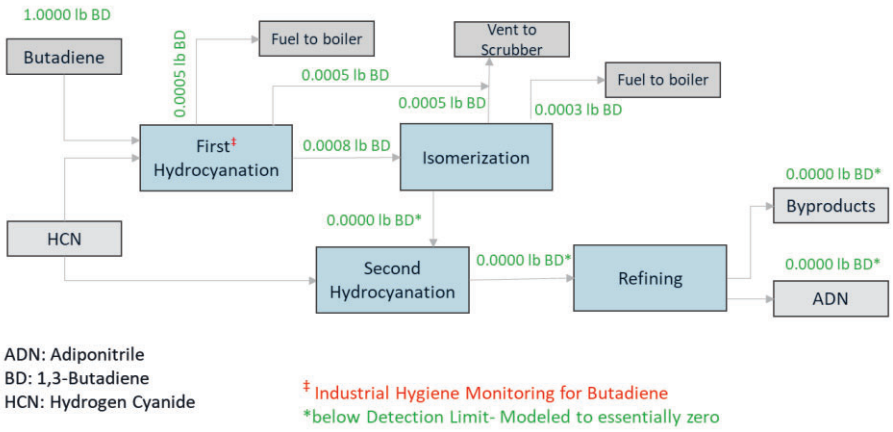
2. Chemical Intermediates Manufacturing Examples

Chemical intermediates starting from 1,3-butadiene include 1,4 Hexadiene, Sulfolane and 1,5,9-Cyclodecatriene [7]. Other industrial chemistries use 1,3-butadiene to make 1-Octene, 1-Octanol, and

Adiponitrile. Newer chemical approaches include those that use catalysts to transform 1,3-butadiene to chemicals such as adipates, adipic acid, and 3-ethyl-6-vinyltetrahydro-2H-pyran-2-one (EVP) [10].

An example of one such chemistry is adiponitrile. 1,3-butadiene is used as a building block chemical to make nylon 6,6 through the adiponitrile process, as shown in Figure 6 [15]. 1,3-butadiene is fed through a closed, tightly monitored system into a hydrocyanation process to form adiponitrile. Any residual 1,3-butadiene vapors during the hydrocyanation process are sent to destruction devices. By the end of the hydrocyanation process, at which point adiponitrile has been created, 1,3-butadiene has been completely consumed and is no longer detectable in the product stream. Adiponitrile is then converted to produce hexamethylene diamine, a nylon intermediate that is used to produce nylon 6,6 polymer.

Figure 6 – Overview of the Adiponitrile Manufacturing Process [15]



H. **What End Products are made from 1-3-Butadiene derived Synthetic Rubbers or Chemical Intermediates**?

Figure 4 in the upper right box lists the most common products that are derived from polymer or chemical intermediates uses. Generally, synthetic rubbers are the starting point for manufacture of articles or components for finished goods. Many chemical intermediates end up as other types of synthetic rubber or resins. Examples include 1,4-Hexadiene to make Ethylene Propylene Diene Rubber and 1,5,9-Cyclodecatriene to make nylon resins.

Products, such as tires, are one or more steps removed from the polymerization process. Final end use products made from polymers use vulcanization or other thermal injection molding processes. This makes it unlikely for unreacted 1,3-butadiene to remain in the final products.

Tires are manufactured using separate compounds for different parts of the tire. The various raw materials, such as PBR or SBR and pigments/other additives, are mixed into a homogenized batch of black material with the consistency of gum. The compounded materials are sent to machines to make sidewalls, treads or other tire parts. The parts are pressed together, making an uncured tire. The final

step is to place the uncured tire in a mold and heat to more than 300°F for 12-15 minutes. This vulcanization step bonds the components together and cures the rubber to its final form. (The US Tire Manufacturers Association's website has a video depicting the process) [11].

See references [5], [7], [16] for more detailed listings of downstream uses or end products derived from 1,3-butadiene.

References

1. NTP (National Toxicology Program). 2021. Report on Carcinogens, Fifteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. https://ntp.niehs.nih.gov/go/roc15 DOI: https://doi.org/10.22427/NTP-OTHER-1003. RoC Profile: 1,3-Butadiene; 15th RoC 2021 (nih.gov) accessed 10/4/2023
2. EPA Document # EPA-740-R-20-011 August 2020 Final Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 (epa.gov) accessed 11/8/2023 at 17:00.
3. National Center for Biotechnology Information. PubChem Compound Summary for CID 7845, 1,3-Butadiene. https://pubchem.ncbi.nlm.nih.gov/compound/1_3-Butadiene. Accessed Nov. 17, 2023.
4. L. M. Miller, Investigation of Selected Potential Environmental Contaminants: Butadiene and Its Oligomers, EPA 560/2-78-008 December 1978; https://nepis.epa.gov/Exe/ZyPDF.cgi/910036J7.PDF?Dockey=910036J7.PDF accessed November 7, 2023.
5. Butadiene Product Stewardship Guidance Manual - American Chemistry Council July 20, 2023, accessed November 7, 2023.
6. Butadiene - Chemical Economics Handbook (CEH) | S&P Global (spglobal.com) March 2023
7. W. C. White, Butadiene production process overview, ***Chem.-Biol. Interact***., 2007, 166, 10–14, ISSN 0009-2797, https://doi.org/10.1016/j.cbi.2007.01.009 accessed 11/7/2023 at 10:45.
8. Laurence W. McKeen, 1 - Introduction to Plastics and Elastomers, Editor(s): Laurence W. McKeen, In Plastics Design Library, Effect of Temperature and other Factors on Plastics and Elastomers (Second Edition), William Andrew Publishing, 2008, Pages 1-39, ISBN 9780815515685, https://doi.org/10.1016/B978-081551568-5.50003-7. Accessed 4 Dec. 2023 (https://www.sciencedirect.com/science/article/pii/B9780815515685500037)
9. Polymer Science Learning Center, https://pslc.ws/. Accessed 20 November 2023.
10. J. Yang, P. Wang, H. Neumann, R. Jaskstell and M. Beller Industrially applied and relevant transformations of 1,3-butadiene using homogeneous catalysts, *Ind. Chem. Mater***.**, 2023,**1**, 155-174 https://pubs.rsc.org/en/content/articlelanding/2023/IM/D3IM00009E. Accessed 20 November 2023.
11. US Tire Manufacturers Association website https://www.ustires.org/how-tire-made. Accessed 21 November 2023.
12. OSHA standard 1910.110 Hazardous Materials: Storage and handling of liquified petroleum gases https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.110 . Accessed 1 December 2023.
13. Eastern Research Group, Locating and Estimating Air Emissions from Sources of 1,3-Butadiene, EPA 454/R-96-008 November 1996 https://www3.epa.gov/ttn/chief/le/butadien.pdf . Accessed 4 December 2023.

14. EPA AP 42, Fifth Edition, Volume I, Chapter 6: Organic Chemical Process Industry, Section 6.10 Synthetic Rubber - August 1982 https://www3.epa.gov/ttn/chief/ap42/ch06/final/c06s10.pdf. Accessed 8 January 2024.
15. 1,3-Butadiene TSCA Risk Evaluation Docket ID EPA-HQ-OPPT-2018-0451-0041. Webinar Meeting between 1,3-Butadiene Risk Evaluation Consortium and EPA held on May 7, 2020. Regulations.gov Accessed 8 January 2024.
16. 1,3-Butadiene TSCA Risk Evaluation Docket ID EPA-HQ-OPPT-2018-0451-0003. Letter from International Institute of Synthetic Rubber Producers, Inc. to EPA dated June 19, 2019. https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0451-0003 Accessed 31 March 2024.

AECOM

Evaluation of EPA TSCA Screening Level Approach

American Chemistry Council
1,3-Butadiene TSCA Risk Evaluation Consortium

April 2024

Delivering a better world

Prepared for:

American Chemistry Council
1,3-Butadiene TSCA Risk Evaluation Consortium

Prepared by:

AECOM
19219 Katy Freeway, Suite 100
Houston, TX 77094
aecom.com

Table of Contents

Figures

Tables

Executive Summary

Under the Toxic Substances Control Act (TSCA), the United States Environmental Protection Agency (US EPA) has a process for ensuring safety of existing TSCA chemicals which involves three stages (Prioritization, Risk Evaluation, and Risk Management). As part of the TSCA Risk Evaluation stage, the EPA published a draft of a proposed screening level methodology to evaluate potential chemical exposures and associated risks to fenceline communities in January 2022 ("Draft Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities", EPA Document# EPA-744-D-22-001, hereinafter referred to as the TSCA Screening Level Approach).

In this report, we assess EPA's proposed approach for making risk determination decisions and informing risk management actions for 1,3-butadiene, and propose refinements to the EPA's approach. Currently, the proposed TSCA Screening Level Approach involves a tiered methodology including a Pre-Screening stage (using EPA's Integrated Indoor-Outdoor Air Calculator – IIOAC), a Full-Screening stage (using EPA's air dispersion model AERMOD), and a Co-resident Screening stage (using EPA's Indoor Environment Concentration in Buildings with Conditioned and Unconditioned Zones model – IECCU). This report only examines the first two stages of the Screening Level Approach as they address outdoor air quality. To evaluate the TSCA Screening Level Approach, a case study facility with reported 1,3-butadiene emissions was chosen. The chosen facility was previously evaluated by the EPA as part of the Office of Air's Residual Risk Assessment for the Miscellaneous Organic Chemical Manufacturing National Emission Standards for Hazardous Air Pollutants (MON) in support of the 2020 Risk and Technology Review (RTR) (Docket EPA-HQ-OAR-2018-0746). Since 1,3-butadiene is a hazardous air pollutant, under the Clean Air Act, it was evaluated in the Residual Risk Assessment.

To assess the TSCA Screening Level approach, we compare the first two stages (Pre-Screening and Full-Screening) to an air dispersion model that is set up following the example provided in the 2020 MON RTR (referred to as facility-specific modeling in this work). This modeling study (i.e. where "modeling study" refers to the Pre-Screening, Full-Screening, and facility-specific AERMOD model) is repeated for the years 2019 and 2021. The modeled maximum concentrations for both years showed similar trends where TSCA Pre-screening (IIOAC) outputs consistently had the highest values (10.75 $\mu g/m^3$ and 9.69 $\mu g/m^3$ for years 2019 and 2021 respectively), followed by the TSCA Full-Screening AERMOD (1.04 $\mu g/m^3$ at the north fenceline receptor or 1200 m from facility's central source and 0.74 $\mu g/m^3$ also slightly north of the fenceline receptor or 1200 m from facility's central source), with the facility-specific AERMOD run producing the lowest output concentrations (0.44 $\mu g/m^3$ at the west fenceline receptor or 1200 m from the facility's central source and 0.46 $\mu g/m^3$ at the east fenceline receptor or 1300 m from the facility's central source).

The modeling studies highlight conservative results from the TSCA Screening Level Approach methodologies, where the concentrations from the Pre-screening stage are an order of magnitude greater than the Full-screening stage, and the Full-screening stage concentrations are almost twice as high as the facility-specific AERMOD run. Examining the modeled concentrations at various receptors extending from near-fenceline to ~5 miles away showed that **concentrations dropped considerably as distance from the facility increased for the TSCA Pre-screen, Full-screen, and the facility-specific models**. The facility-specific AERMOD following the EPA's 2020 MON RTR methodology, which is considered the best available science, produced the most predictive (albeit still conservative) concentrations of all three models, because it utilized the most specific multi-variable inputs.

Facilities that produce or use 1,3-butadiene are also regulated under the MON and Hazardous Organic NESHAP (HON) rules. Accordingly, this report highlights potential air quality impacts of emissions from the case study facility using predicted post-MON concentrations provided in the 2020 MON RTR docket. Additionally, there is a qualitative discussion of impacts on 1,3-butadiene concentrations after the final HON rule is promulgated in early 2024.

Since 1,3-butadiene has multiple sources and arises from various sources other than manufacturing and/or use, monitoring data can more accurately represent air concentrations at which communities are exposed. To put the air dispersion modeling studies into context, ambient air concentrations of 1,3-butadiene measured at various nationwide sites with automated gas chromatography (auto-GC) measurements from years 2017 to 2021 are analyzed. All average concentrations (with the exception of one Texas site in 2021) were found to be below 1 ppb.

This case study highlights the conservative results from the methodologies proposed in the TSCA Screening Level Approach. Using facility-specific data, a more refined air dispersion model run produces modeled concentrations that are more realistic and more closely match with ambient measurements.

1. Introduction/Background

1.1 EPA Toxic Substances Control Act

Under the Toxic Substances Control Act (TSCA), the United States Environmental Protection Agency (US EPA) has the authority to issue regulations which collect health/safety and exposure information, require testing, and control exposure to chemical substances and mixtures. Specifically, TSCA requires that the EPA maintain the TSCA Chemical Substances Inventory, require testing of chemical substances to evaluate health or environmental hazards, regulate the manufacture, processing, distribution, use, and/or disposal of any chemical that may present an unreasonable risk of injury to human health or the environment, and finally coordinate actions on TSCA-controlled substances with actions under other federal laws, including laws administered by other federal agencies or other laws administered by EPA.[1]

1.1.1 Risk Evaluation for Existing Chemicals

The three stages of the EPA's process for ensuring safety of existing TSCA chemicals are (1) Prioritization, (2) Risk Evaluation, and (3) Risk Management. The purpose of the Risk Evaluation step (which is addressed in this report) is to determine whether a chemical presents unreasonable risk to human health or the environment, including risk to a "potentially exposed or susceptible subpopulation"[2]. To inform Risk Evaluation, in January 2022, the EPA published a draft version of a proposed screening level methodology to evaluate potential chemical exposures and associated risks to fenceline communities ("Draft Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities", EPA Document# EPA-744-D-22-001).[3]

In this report, we examine the suitability of the TSCA Screening Level Approach for informing risk determination decisions and risk management actions for one of the TSCA chemicals that is also a hazardous air pollutant, namely 1,3-butadiene. Facilities that produce or use 1,3-butadiene are also regulated under two other EPA rules: (1) the national emission standards for hazardous air pollutants (NESHAP) for the miscellaneous organic chemical (MON) manufacturing industry, and (2) the NESHAP for synthetic organic chemical manufacturing industry (SOCMI), commonly known as the hazardous organic NESHAP rule (HON).

Currently, the EPA's TSCA Screening Level Approach involves a tiered screening methodology summarized in Figure 1.

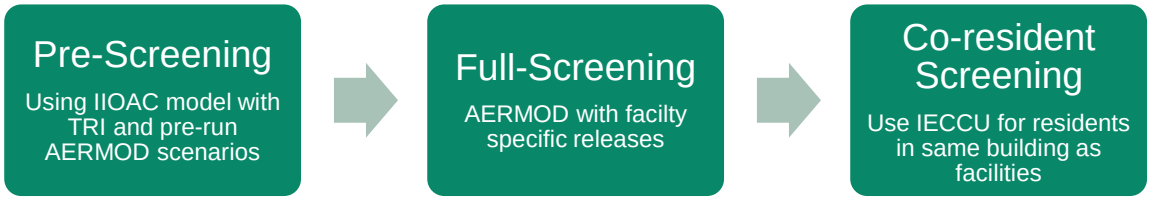


Figure 1: Tiered screening adapted from EPA's TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities

This work aims to present a refinement of the proposed methodology in the TSCA Screening Level Approach, that is a more streamlined approach for the EPA to carry out the risk evaluation in a fit-for-purpose manner. The proposed refined approach is tiered, with increasing level of complexity and data requirements, only if the prior generic/conservative tier suggests unreasonable risk. Additional analysis with measured data would be conducted to further refine the predicted exposures. Figure 2 shows the proposed refinement of the TSCA Screening Level Approach for industrial facilities. Co-residential exposures are not considered in this work as they involve indoor air analysis whereas the scope of this work is ambient modeling and measurements.

[1] EPA TSCA webpage: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/
[2] TSCA Risk Evaluation webpage: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca
[3] Draft TSCA Screening Level Approach document: https://www.epa.gov/system/files/documents/2022-01/draft-fenceline-report_sacc.pdf

This work aims to assess the feasibility of carrying out the refined tiered screening approach presented in Figure 2. To do so, we selected a case-study facility which is known to produce and/or use 1,3-butadiene and carried out the modeling and analysis presented in the refined methodology.

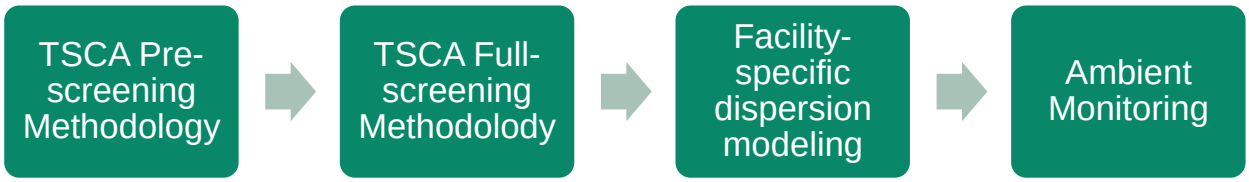


Figure 2: Proposed refinement of the tiered screening for industrial facilities (not for co-residential exposures)

1.1.2 Selection of Case Study facility

Consistent with EPA's commitment to leverage existing data, the selected case-study facility was previously evaluated as part of the EPA's Residual Risk Assessment for the MON in support of the 2020 Risk and Technology Review[4,5]. The chosen facility is a site in the Houston area which is known to have several neighboring industrial 1,3-butadiene sources and some non-industrial sources (such as traffic) given its location in an urban area. It is located near the Houston Ship Channel which is an area that has been the subject of several studies on air toxics including 1,3-butadiene[6,7,8] due to the presence of many oil refineries, chemical processing plants, and numerous major highways in proximity to residential areas. Additionally, the site is located near several air monitoring sites which record hourly 1,3-butadiene concentrations using automated gas chromatographs.

Figure 3 shows the locations of several 1,3-butadiene-emitting facilities (orange circles) and the nearest air monitoring sites (black kites) in the Harris County area. In the following sections of the report, a few key sites (shown on the map) will be discussed. The chosen facility is directly northwest of the HRM-16 air monitoring site. The Milby Park air monitoring site is located close to a number of 1,3-butadiene-emitting facilities, whereas the HRM-3 air monitoring site is at least 5 km away from the nearest 1,3-butadiene emitting facility. The chosen facility fenceline (shown in Figure 4) represents the location where the maximum emissions are measured, HRM-16 represents the location where slightly lower but still "high-end" concentrations may be detected, and the HRM-3 location represents an off-site location that should be minimally impacted by 1,3-butadiene emissions from neighboring facilities. Information on the Houston Regional Monitoring (HRM) network of air monitoring sites can be found through their website.[9]

[4] https://www.regulations.gov/document/EPA-HQ-OAR-2018-0746-0189
[5] MON Final Rule: https://www.federalregister.gov/documents/2020/08/12/2020-12776/national-emission-standards-for-hazardous-air-pollutants-miscellaneous-organic-chemical
[6] Air Pollutant Mapping with a Mobile Laboratory During the BEE-TEX Field Study: https://journals.sagepub.com/doi/pdf/10.4137/EHI.S15660
[7] Modeling of 1,3-butadiene in urban and industrial areas: https://www.sciencedirect.com/science/article/abs/pii/S1352231014009042
[8] Uncertainties in Air Toxics Calculated by the Dispersion Models AERMOD and ISCST3 in the Houston Ship Channel Area: https://journals.ametsoc.org/view/journals/apme/46/9/jam2540.1.xml
[9] HRM Houston Regional Monitoring - https://hrm.aecom.com/sitemap.htm

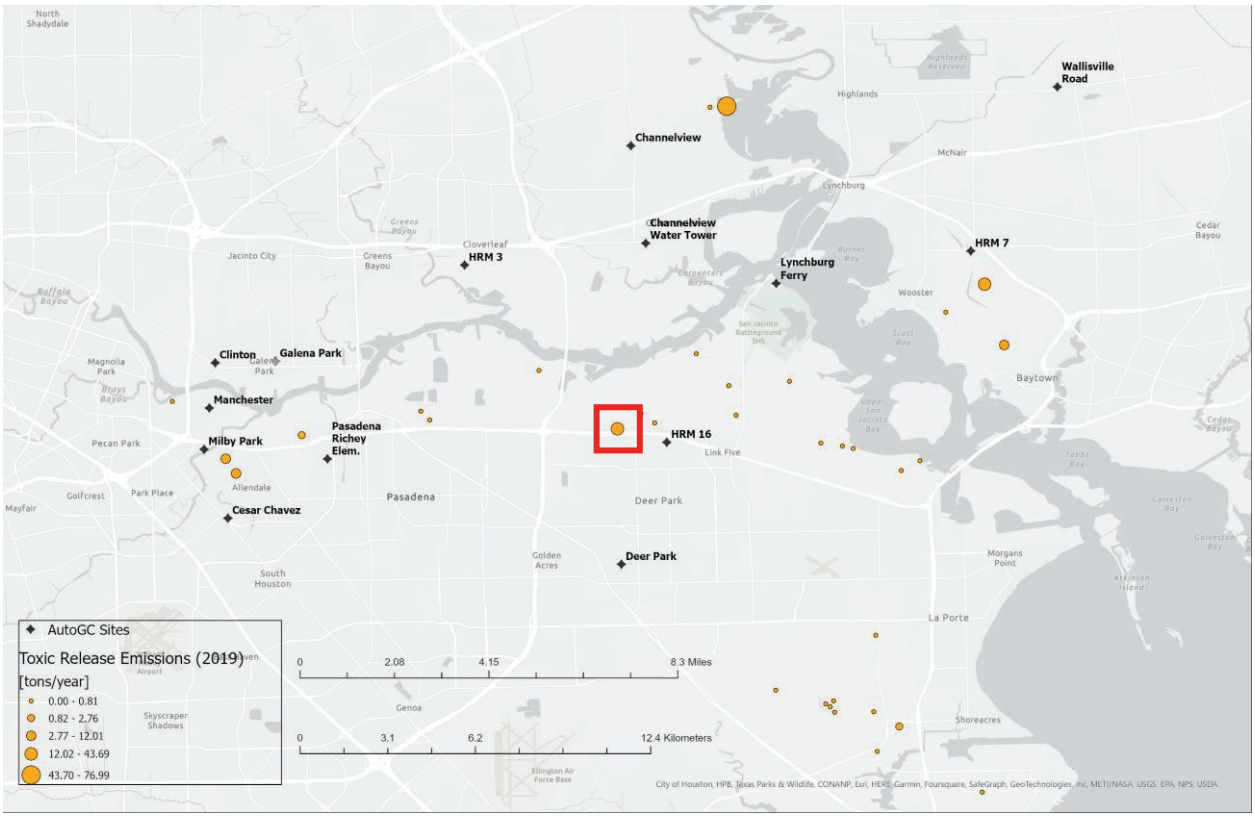


Figure 3: Map showing locations of Milby Park and HRM-3 sites in Houston, relative to neighboring TRI facilities with reported 1,3-butadiene emissions

This work presents the modeling study of this facility for the years 2019 and 2021, as well as for year 2019 data with predicted post-MON reductions based on the 2020 MON final rule[5]. The "modeling study" refers to the models described in Boxes 1, 2, and 3 shown in Figure 2. This work also provides a qualitative summary of potential emissions reductions based on the 2023 proposed HON rule, which is anticipated to be finalized by March 29, 2024[10]. Details on each of the models used in this work, as well as ambient air monitoring (Box 4) results, are presented in the following sections of the report.

Note that this work builds on previous verbal and written comments[11,12] submitted by the American Chemistry Council addressing the suitability of the TSCA Screening Level Approach.

2. TSCA Screening Level Approach

The TSCA Screening Level Approach describes tiered methodologies that are used to estimate ambient air concentrations and exposures for members of the public that are located between 5 to 10,000 meters from emission sources. Two of the three methodologies are the Ambient Air Pre-screening Methodology and the Ambient Air Full-screening Methodology. The third tier which is the Ambient Air Co-resident Screening Methodology is used to determine indoor air exposures for receptors living above or adjacent to a releasing facility. This report will focus on the outdoor air concentrations/exposures only; the third methodology is beyond the scope of this work. Additionally, the case-study facility is not located in a building with residents.

[10] https://www.federalregister.gov/documents/2023/04/25/2023-07188/new-source-performance-standards-for-the-synthetic-organic-chemical-manufacturing-industry-and
[11] Previous comments from ACC: https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0415-0066
[12] Previous comments from ACC: https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0415-0086

1.2 Pre-screening Integrated Indoor-Outdoor Air Calculator

The first methodology which is known as the Ambient Air Pre-screening Methodology is used to estimate ambient air concentrations and associated exposures based on maximum and mean releases of emitted chemicals. This methodology is independent of facility and use classifications, and results from this methodology are intended to inform the need for a full-screening level analysis. The pre-screening methodology utilizes EPA's Integrated Indoor/Outdoor Air Calculator (IIOAC) model[13] to estimate high-end (95th percentile) and central-tendency (mean) exposures to select receptors at pre-defined distances from a releasing facility (100, 1000 meters). The IIOAC estimates indoor and outdoor concentrations using pre-run results from a dataset of air dispersion scenarios that were run in a variety of meteorological and land-use settings within AERMOD. To run this Excel-based tool, several input parameters are required as discussed in the following section.

1.2.1 IIOAC Inputs

The following table presents parameters that are potential inputs for the IIOAC tool. Note that the parameters required/used for the modeling study in this report are in bold font.

Table 1: Input parameters for TSCA Pre-screening Methodology (IIOAC)

Emission Parameters • Source Type (e.g. **Point**, **Fugitive**, Area Water, Area Soil) • Duration of release (e.g. 1, 4, 8, **24 hours/day**) • **Mass Released per day (kg/day)** • **Release days per year**
System-specific Parameters • **Surface Area (m^2)** • Depth of water (m) • Flowrate (m^3/day)
Chemical-specific Parameters • **Chemical Name** • **CAS Number** • Vapor pressure (Torr) • Solubility (mg/L) • Organic carbon sorption coefficient (mL/g) • Volatilization half-life (1/day) • Molecular weight (g/mol)
Urban or rural setting
Particle size or **vapor** (only required for Point and Fugitive source types)
Climate Region (Specified in Guidance) • IIOAC uses one of fourteen conservatively developed meteorological datasets (e.g. Lake Charles, LA for South (Coastal) region) • Data sets are from years 2011 to 2015
Receptors pre-set by IIOAC (Specified in Guidance) Two groups: Inner ring "fenceline" receptors (~100 m from source), near-facility "community" receptors (~1000 m from source)

The TSCA Screening Level Approach calls for the use of EPA's Toxic Release Inventory (TRI)[14] data for the year of interest when finding emission rate values. The two years that were chosen for the modeling analyses in this report are 2019 and 2021. Year 2019 was chosen as a recent year that is representative of a period with regular weather conditions and industrial/vehicular activity patterns, and Year 2021 was chosen as an example of a year with a force majeure event (i.e. Winter storm Uri in Texas). For this report, 2019 and 2021 TRI data was extracted for facilities releasing 1,3-

[13] IIOAC webpage: https://www.epa.gov/tsca-screening-tools/iioac-integrated-indoor-outdoor-air-calculator
[14] TRI webpage: https://www.epa.gov/toxics-release-inventory-tri-program

butadiene. The particular case-study facility that was chosen for this report is a facility in the Houston area that emits 1,3-butadiene and is surrounded by a number of industrial and non-industrial 1,3-butadiene sources. The site is also located near several air monitoring stations which record 1,3-butadiene concentrations using automated gas chromatographs. This particular site exists within a single property boundary where four different companies operate. Of these four operators, two have reported 1,3-butadiene emission rates to the EPA's TRI. For the facilities of interest (TRIFD 77536SHLLLHIGHW and 77536DRPRK5900H) within the single property boundary, values for the FUGTIVE-AIR category (in pounds per year) were added and converted to the required IIOAC input units of kg/day assuming continuous year-long operation (24 hours/day, 7 days/week). The same was done for the STACK-AIR category. The FUGITIVE-AIR emission rates were used as inputs for the IIOAC run with Fugitive source type, and the STACK-AIR emission rates were used as inputs for the IIOAC run with the Point source type.

1.3 Full-screening Dispersion Model

The second methodology described by the TSCA Screening Level Approach document is known as the ambient air full-screening methodology. This methodology utilizes AERMOD to estimate concentrations at user-defined distances from a facility releasing a chemical that is undergoing risk evaluation, i.e. 1,3-butadiene in this report. AERMOD (American Meteorological Society/Environmental Protection Agency Regulatory Model) is an air dispersion model developed by the American Meteorological Society and the EPA's Regulatory Model Improvement Committee that is used for assessing air quality impacts near industrial sources of air pollution. The EPA requires the use of this refined dispersion model for State Implementation Plan (SIP) revisions for existing sources and for New Source Review (NSR) and Prevention of Significant Deterioration (PSD) programs.[15]

The TSCA Full-Screen methodology can be utilized after the pre-screening IIOAC tool, or independent of it, and is meant to provide a more thorough analysis than the pre-screening methodology to allow EPA to fully characterize identified risks for chemicals undergoing risk evaluation.[16]

1.3.1 TSCA Full-screening AERMOD ("Simplified AERMOD") Inputs

The following table presents the parameters that were used to set up the AERMOD run for the Full-screening methodology, following the guidance provided in the TSCA Screening Level Approach[17].

Figure 4 shows a screenshot of the AERMOD GUI software used for this analysis (BEEST) and captures the facility fenceline (blue border), single point and single area sources at the center of the facility, and a polar receptor grid extending from within the facility boundary up to 10 km beyond the fenceline. Discrete receptor points were added at coordinates corresponding to HRM-3 and HRM-16 air monitoring sites to investigate modeled concentrations at a near-source or near-fenceline location (HRM-16), and an off-site location downwind of the modeled facility (HRM-3), and to allow for comparison of modeled concentrations with ambient air monitoring data at both sites.

Note that the TSCA Full-screening approach is referred to as a "Simplified AERMOD" run throughout this report due to its consolidation of emission rates from all sources into one point source and one area source, and its use of preset source physical characteristics, as discussed in Table 2.

Table 2: Input parameters for TSCA Full-screening (Simplified AERMOD)

Emission Rates/Locations • Rates for Point and Area sources obtained from 2019 and 2021 TRI datasets (Facility TRIFD 77536SHLLLHIGHW and 77536DRPRK5900H) • Facility emissions centered on one location assigned coordinate of (0,0) (not based on actual release point locations of singular sources) • (0,0) coordinate represents latitude/longitude information reported to TRI
Source physical characteristics 1 POINT (Stack) source with: • Stack Height = 10 m

[15] https://www.epa.gov/scram/air-quality-dispersion-modeling-preferred-and-recommended-models
[16] Section 2.1.2.2 (page 30) of TSCA Screening Level Approach guidance (EPA Document# EPA-744-D-22-001)
[17] Page 58 of TSCA Screening Level Approach guidance (EPA Document# EPA-744-D-22-001)

- Stack Diameter = 2 m
- Exit Temperature = 300 Kelvin
- Exit velocity of 5 m/s

1 AREA (Fugitive) source with:

- 10x10 m ground-level area source per facility
- Release height = 3.05 m
- Point and fugitive source are co-located
- Above assumptions are made since TRI data does NOT include source-specific physical characteristics, but facility-level emissions only

Meteorological Data

- Use meteorological dataset from closest meteorological station within EPA database of 824 stations
- Closest station to chosen facility with William P. Hobby Airport (HOU), which had pre-processed data available from TCEQ website[18]
- 2021 and 2019 HOU meteorological data with *low* surface roughness was used based on AERSURFACE run at facility site

Receptors

- Receptor distance up to 10 km from facility boundary
- Option of polar- or centroid-based receptor grid
- For (default) polar grids, set receptor grid as 16 radials (every 22.5°), and 13 rings
- Discrete receptor points added at HRM-3 and HRM-16 sites
- Flagpole height for all receptors = 1.8 m
- Flat terrain assumed

Urban setting

[18] TCEQ pre-processed meteorological datasets: https://www.tceq.texas.gov/permitting/air/modeling/aermod-datasets.html

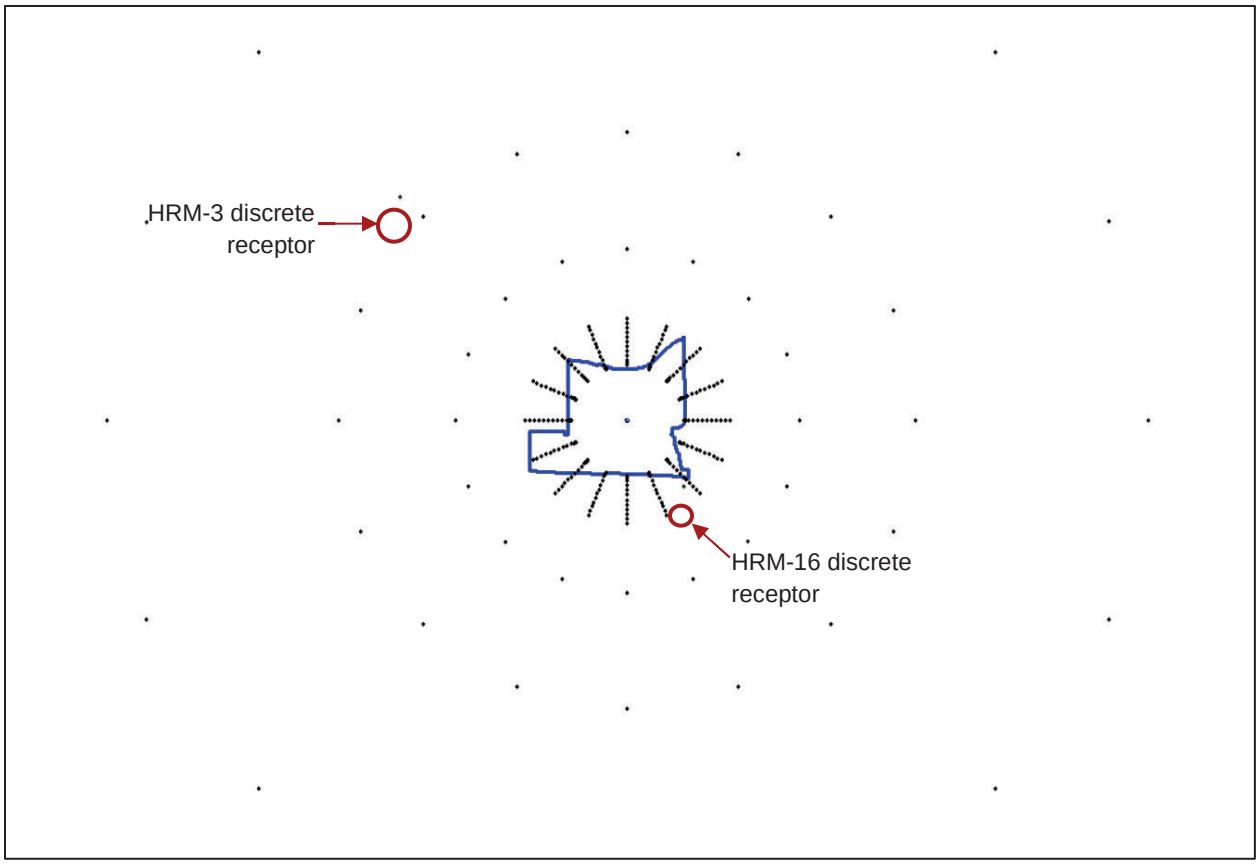


Figure 4: Snippet of BEEST input setup for TSCA full-screening methodology (sources at central point, blue fenceline, polar receptor grid)

3. Facility-Specific Dispersion Modeling

1.4 Permit-style Dispersion Modeling

Modeled output concentrations from the TSCA full-screening methodology (simplified AERMOD) can be compared to AERMOD runs following the EPA's method of AERMOD setup used in the Residual Risk Assessment review for the 2020 MON RTR final rule[4]. The EPA's AERMOD setup used in the MON RTR is similar to the dispersion model setup suggested by the TCEQ's Air Permits Division Air Quality Modeling Guidelines (APDG 6232, November 2019)[19]. The following section of this report discusses the required inputs for an air dispersion model setup following the EPA's MON RTR approach and TCEQ guidance (also referred to as "permit-style" dispersion model in this work).[19] Later sections of this report compare model outputs from the TSCA Full-screening methodology (simplified AERMOD) and the "permit-style" (facility-specific AERMOD) run. It is useful to note here that the permit-style AERMOD run is considered the best available science as it utilizes the EPA's preferred dispersion model for modeling steady-state plumes, and incorporates a necessary level of detail when dealing with model inputs, as seen in the 2020 MON RTR.

1.4.1 Permit-style (Facility-specific AERMOD) Inputs

The following table presents the parameters that were used to set up the AERMOD run for the permit-style model run, following the guidance provided in the TCEQ Air Permits Division Air Quality Modeling Guidelines[19] and the latest MON RTR. Figure 5 shows a screenshot of model setup in the BEEST software and captures all point (red dots) and area (blue boxes) sources, and the receptor grid modeled after TCEQ guidelines as discussed in detail in Table 3. Discrete

[19] TCEQ Air Quality Modeling Guidelines: https://www.tceq.texas.gov/assets/public/permitting/air/Modeling/guidance/airquality-mod-guidelines6232.pdf

receptor points were added at coordinates corresponding to HRM-3 and HRM-16 air monitoring sites to investigate modeled concentrations at a near-source location (HRM-16, not shown in Figure 5), and an off-site location downwind of the modeled facility (HRM-3), and to allow for comparison of modeled concentrations with ambient air monitoring data at both sites.

Table 3: Input parameters for permit-style model (Facility-specific AERMOD)

Emission Rates/Locations

- Rates for Point and Area sources obtained from 2020 National Emission Inventory (NEI)[20] for the 2021 model study, and from EPA 2019 modeling files[21] for the 2019 model study (Facility ID 4168511, corresponding to Facility TRIFD 77536SHLLLHIGHW and 77536DRPRK5900H)
- Coordinates for point and area sources provided in 2020 NEI and 2019 modeling file (based on actual release points)
- Total site emissions from multiple owners/operators

Source physical characteristics

72 point sources with the following source-specific parameters entered based on 2020 NEI or 2019 EPA modeling data:

- Stack Height
- Stack Diameter
- Exit Temperature
- Exit velocity

26 area sources with the following source-specific parameters entered based on 2020 NEI or 2019 EPA modeling data:

- Release area
- Release height
- Fugitive Easterly/Northerly length

Meteorological Data

- On-site meteorological data used from TCEQ site (HRM-16) near the facility (0.82 miles southeast of facility)
- Closest station to chosen facility with William P. Hobby Airport (HOU), which had pre-processed data available from TCEQ website[22]
- Upper Air data from Lake Charles, Louisiana (closest site with data availability)[23]
- Surface data, 1-minute, and 5-minute Automated Surface Observing Systems (ASOS) from William P. Hobby (KHOU) airport[24]
- AERMINUTE run using KHOU 1-minute and 5-minute data (2019, 2021)
- AERSURFACE run for Primary location (HRM-16, i.e., onsite meteorological data site), and Secondary location (KHOU)
    - Land Cover/Impervious/Tree Canopy files for surface characterizations based on National Land Cover Database (NLCD)[25] data
- AERMET Stage 1 and Stage 2 runs completed successfully (separate for 2019 and 2021 data)
- Output profile (.pfl) and Surface file (.scf) generated for input into AERMOD

Receptors

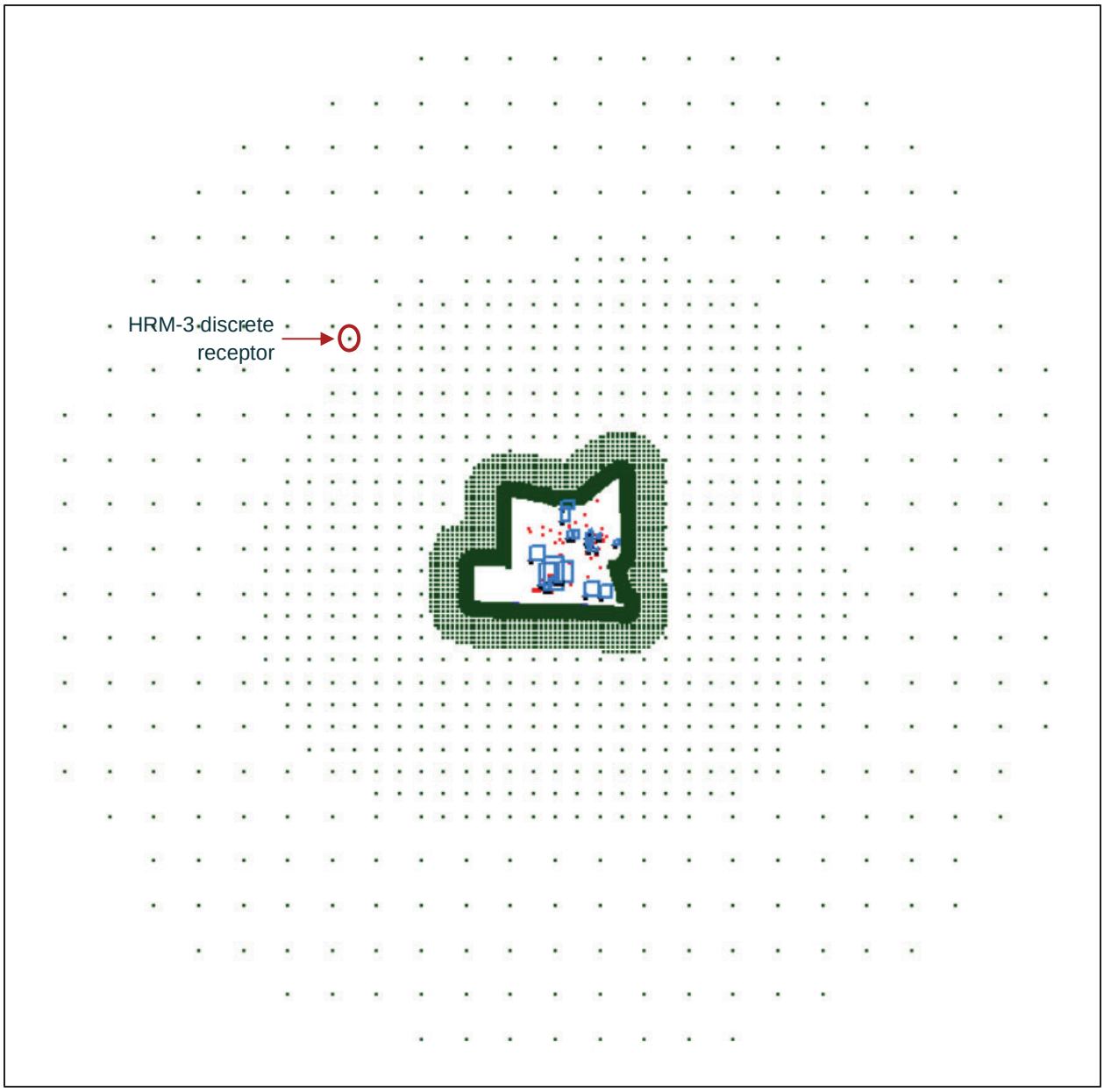
- Fenceline determined by examination of facility aerial imagery
- Receptor grid designed based on TCEQ Air Quality Modeling Guidelines (APDG 6232)
- Tight receptors spaced 25 meters apart; extending up to 300 m from facility
- Fine receptors spaced 100 meters apart; extending up to 1 km from facility
- Medium receptors spaced 500 meters apart; extending up to 5 km from facility
- Coarse receptors spaced 1 km apart; extending up to 50 km from facility
- Discrete receptor points added at HRM-3 and HRM-16 sites

Urban setting

To provide additional context to the meteorological dataset synthesis for the permit-style AERMOD run, on-site meteorological data from the TCEQ monitoring site neighboring the chosen facility – HRM-16 – was used. One year (2019 and 2021) hourly data from HRM-16 which included wind speed (mph), wind direction (degrees), temperature

[20] EPA 2020 NEI data webpage: https://www.epa.gov/air-emissions-inventories/2020-national-emissions-inventory-nei-data
[21] EPA 2019 Emissions Modeling webpage: https://www.epa.gov/air-emissions-modeling/2019-emissions-modeling-platform
[22] TCEQ pre-processed meteorological datasets: https://www.tceq.texas.gov/permitting/air/modeling/aermod-datasets.html
[23] Data accessed from NOAA/ESRL Radiosonde Database: https://ruc.noaa.gov/raobs/
[24] Data access: https://www.ncei.noaa.gov/pub/data/noaa/ and https://www.ncei.noaa.gov/pub/data/asos-onemin/
[25] NLCD Land Cover/ Impervious/Tree canopy files obtained from https://www.mrlc.gov/viewer/

(°F), pressure (inHg) was downloaded from the TCEQ's TAMISWeb database.[26] Gaps in data of 4 hours or less were supplemented with interpolated data from the HRM-16 site. Gaps in data greater than 4 hours were supplemented with meteorological data from the TCEQ's Houston Deer Park site (5.02 km away from Hexion Deer Park facility).



[26] TAMISWeb webpage: https://www17.tceq.texas.gov/tamis/index.cfm

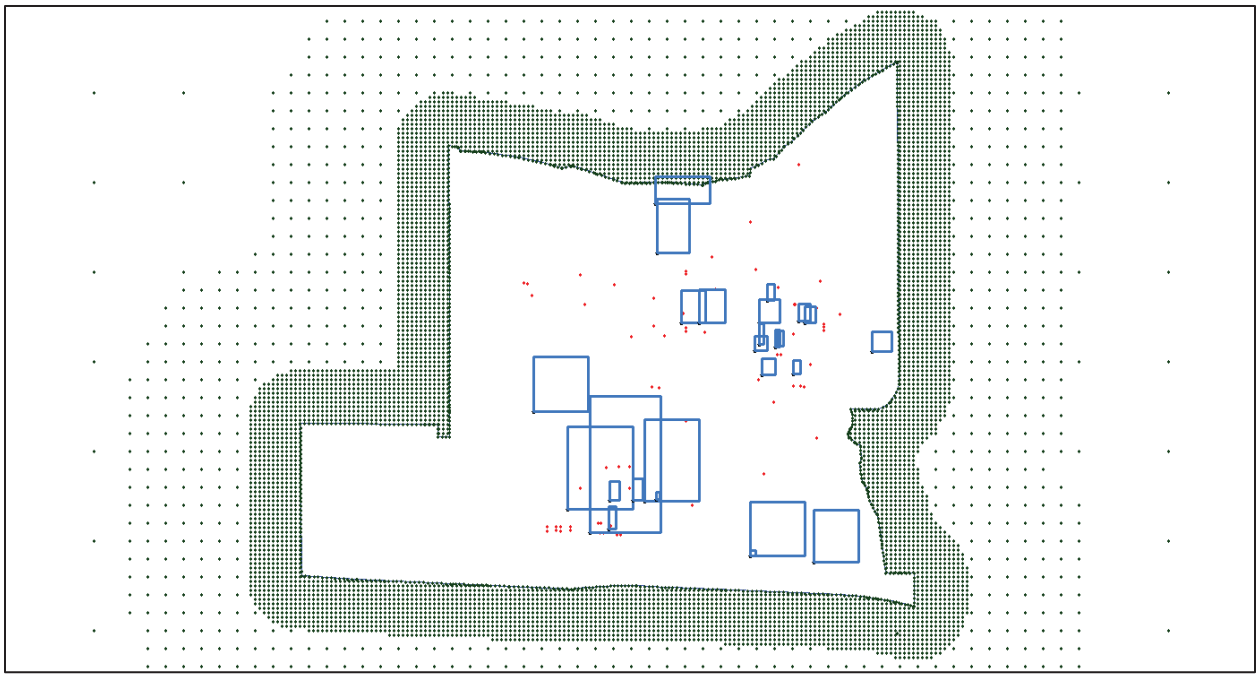


Figure 5: Snippets of BEEST input setup for permit-style model (including full receptor grid, and zoomed in to show sources)

It is important to note here the difference between the sources for emission rates used in the TSCA Full-Screen model, i.e. facility-wide emission rates reported to the TRI, compared to the Facility-Specific AERMOD, i.e. source-specific emissions rates reported to the NEI. To provide context on the difference between the two EPA-managed databases, the NEI is a comprehensive emissions inventory that tracks air pollutants from various sources including stationary sources (such as industrial facilities), mobile sources (such as traffic), and other nonpoint and area sources. TRI is a publicly available databased containing information on the release and transfer of toxic chemicals only from industrial facilities across the United States. Not all industrial facilities are required to report to TRI; only those that meet specific criteria outlined by the Environmental Protection Agency (EPA) must report their toxic releases and waste management activities. The same is true for facilities reporting to the NEI; only those facilities that exceed certain emission rates in a year are required to report a yearly emissions inventory to their state environmental agency.

A joint report published by the EPA and several state, local, and tribal environmental agencies (SLTs) [27] explored the difference between the two EPA-managed databases in more depth. Some of the overarching findings indicate that:

1. The NEI includes more facilities (88,000 facilities) than the TRI (22,000 facilities)
2. ~50% of facilities that report to the TRI also report to the NEI (10,238 out of 20,258 facilities)
3. When summed across all facilities, roughly half of pollutant emission rates agree within 10% (and three quarters of pollutants agree within 20%)
4. When comparing the emissions of pollutants by individual facilities, roughly half of the TRI and NEI rates are within 10% of each other
5. Out of a total of 4,797 records where TRI and NEI emissions were comparable (i.e. within 2% of one another), approximately 27% had noticeable differences in how emissions were allocated to stack and fugitive releases.

For the refined modeling tier, TRI data can be used to verify the quality of the NEI data or gap-fill NEI data, as recommended in the joint EPA and SLT report[27]. The reason for recommending the use of NEI data for the refined tier (Facility-specific AERMOD) is that TRI data lacks necessary detail on release parameters for stack and fugitive sources (e.g. stack height, stack temperature, exit velocity, area release height, etc.). The EPA is aware that stack height has the greatest impact on predicted air pollutant concentrations, where a 40-meter median stack height compared to a 10-meter median stack height reduces peak concentration by a factor of 20 and the peak occurs 4 times further downwind[28,29]. Using the more granular or source-characterized data from the NEI provides improved inputs for a more

[27] https://www.epa.gov/sites/default/files/2019-02/documents/final-report-phase2-tri-nei-slt.pdf
[28] Comment in EPA docket: https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0415-0086
[29] https://www.epa.gov/rsei/estimate-stack-heights-and-exit-gas-velocities-tri-facilities-oppts-risk-screening

accurate risk evaluation. In addition, the NEI has been rated as a high-quality data source according to the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances*[30], making it a reliable source of inputs for the proposed Facility-specific AERMOD.

1.4.1.1 Choice of AERMOD Graphical User Interface

For this modeling exercise, AERMOD was run using BEEST which is a graphical user interface (GUI) for AERMOD, sold and maintained by Providence Oris[31]. The regulatory default option was selected when running AERMOD using BEEST and no "BETA" options were used. Other commonly used GUIs used to run AERMOD include Lakes Environmental Software AERMOD View[32] and Trinity Consultants' BREEZE AERMOD GUI[33]. The use of a graphical user interface to facilitate setting up model inputs and analyzing model results does not affect model concentrations, especially when the AERMOD model code is not altered. Recent guidance from the EPA highlights that if changes are made to a preferred model (such as AERMOD) without affecting modeled concentrations, the preferred status of the model is unchanged. In this case, the use of a GUI is an example of a modification that does not affect model concentrations.[34]

Another model that is used primarily for performing risk assessments for sources emitting air toxics to ambient air is the EPA's Human Exposure Model (HEM)[35]. HEM only addresses the inhalation exposure pathway and is designed to predict the risk associated with chemicals emitted into the ambient air, which is defined as the vicinity of a facility but beyond its property boundary. The current version of HEM (HEM 4.2) includes (1) AERMOD as the atmospheric dispersion model, with included pre-processed meteorological data, (2) US Census Bureau population data at the Census block level (currently using 2020 data). The AERMOD code included in HEM-4 is the same as that used in the aforementioned GUIs, so output concentrations from HEM (estimated in micrograms per cubic meter) should be unchanged across these softwares. The main difference is that HEM-4 extends the exposure estimates by combining them with pollutant health reference values to estimate cancer risks and noncancer hazards, among other risk measures.

[30] https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0005
[31] https://www.providenceoris.com/product/beest-suite/
[32] https://www.weblakes.com/software/air-dispersion/aermod-view/
[33] https://www.trinityconsultants.com/software/dispersion/aermod
[34] https://www.federalregister.gov/documents/2023/10/23/2023-22876/guideline-on-air-quality-models-enhancements-to-the-aermod-dispersion-modeling-system
[35] https://www.epa.gov/fera/risk-assessment-and-modeling-human-exposure-model-hem

1.4.2 Results

Table 4 shows the input values to the IIOAC and TSCA Full Screening Model which are based on reported emission rates to the 2019 and 2021 Toxic Release Inventory. Table 5 and Table 6 show results of the TSCA Pre-screening (Box 1 shown in Figure 2) and Full-screening (Box 2 shown in Figure 2) models (IIAOC and "Simplified AERMOD") compared to a permit-style AERMOD run (Box 3 shown in Figure 2) (i.e. a dispersion model run following the example provided in the EPA's RTR for the 2020 MON final rule (Docket EPA-HQ-OAR-2018-0746)[36] for the years 2019 and 2021. Note that within the IIOAC tool, high-end values are defined as the 95th percentile result, whereas AERMOD results are the "maximum" which is defined as the maximum annual result averaged over one year for the given receptor points (extending from fenceline to 10 km out).[37] Note that in Table 5 and Table 6, the concentrations are provided in μg m^{-3} with corresponding ppb values provided in parentheses. Contour plots showing output concentrations for Box 2 and Box 3 models for Years 2019 and 2021 are available in Appendix A.

Table 4: Toxic Release Inventory (TRI) emission rates, used as inputs to AERMOD (IIOAC and TSCA Full Screen model)

TRI Reporting Year	"AIR-STACK" Category Emission Rate (lbs/year)	"AIR-FUGITIVE" Category Emission Rate (lbs/year)
2019	49,000	5720
2021	42,000	5330

Table 5: Box 1 to Box 3 Model Study Results for Year 2019

Unit: μg/m^3 (ppb)	TSCA Pre-screening IIOAC Point | Area		TSCA Full-screening (Simplified AERMOD)	Permit-style (Facility-specific AERMOD)
Fenceline concentration (high-end)	4.37 (1.97)	6.38 (2.87)		
Community concentration (high-end)	1.22 (0.55)	0.44 (0.20)		
Model Maximum concentration			1.04 (0.47)	0.44 (0.20)
HRM-3 Receptor concentration			0.06 (0.03)	0.04 (0.02)
HRM-16 Receptor concentration			0.12 (0.05)	0.05 (0.02)

Table 6: Box 1 to Box 3 Model Study Results for Year 2021

Unit: μg/m^3 (ppb)	TSCA Pre-screening IIOAC Point | Area		TSCA Full-screening (Simplified AERMOD)	Permit-style (Facility-specific AERMOD)
Fenceline concentration (high-end)	3.75 (1.69)	5.94 (2.67)		
Community concentration (high-end)	1.04 (0.47)	0.41 (0.18)		
Model Maximum concentration			0.74 (0.33)	0.46 (0.21)

[36] EPA MON RTR Supporting documents: https://www.regulations.gov/document/EPA-HQ-OAR-2018-0746-0189
[37] IIOAC 1.0 users guide: https://www.epa.gov/sites/default/files/2019-06/documents/iioac_1.0_users_guide_may_2019.pdf

HRM-3 Receptor concentration		0.04 (0.02)	0.03 (0.01)
HRM-16 Receptor concentration		0.11 (0.05)	0.04 (0.02)

Building on the discussion on TSCA screening model inputs in sections 1.2.1 and 1.3.1, the 2019 TRI data for the chosen facility had a total emission rate of 49,000 lbs/year for point ("stack") sources, and 5720 lbs/year for fugitive sources. The 2021 TRI data for the facility showed a total emission rate of 42,000 lbs/year for point sources, and 5330 lbs/year for fugitive sources. The IIOAC fenceline and community output concentrations are accordingly similar for years 2019 and 2021, with slightly higher output concentrations for 2019 corresponding to the higher reported TRI emissions for that year. Focusing on year 2019 (the year with higher emission rates), adding IIOAC output concentrations from point (4.37 µg m^{-3}) and area (6.38 µg m^{-3}) sources result in a high-end fenceline concentration of 10.75 µg/m^3 (4.84 ppb) and a high-end community concentration of 1.66 µg/m^3 (0.75 ppb). Additionally, as detailed in the forthcoming section of this report, the measured annual average concentration of 1,3-butadiene for the year 2019 at the HRM-16 (near-fenceline) site was 0.393 µg/m^3 or 0.18 ppb. This is considerably lower (<4%) than the predicted-IIOAC fenceline value, which highlights the overly conservative results of this prescreening tool. A similar analysis for the year 2021 IIOAC output concentrations shows that the measured annual average concentration (0.389 µg/m^3 or 0.18 ppb) at HRM-16 (near-fenceline) is less than 5% of the IIOAC-predicted high-end fenceline concentration of 9.69 µg/m^3 or 4.36 ppb(which is based on the sum of the point – 3.75 µg m^{-3} – and area – 5.94 µg m^{-3} – source output concentrations).

Expanding on the locations of the modeled maximum concentrations, the 2019 TSCA Full-Screening AERMOD gave an output maximum concentration of 1.04 µg/m^3 at the north fenceline receptor (1200 m from facility's central source). The 2021 TSCA Full-Screening AERMOD gave an output maximum concentration of 0.74 µg/m^3 also north of the fenceline receptor (1200 m from facility's central source). The 2019 facility-specific AERMOD run produced the lowest output concentrations of all three models (0.44 µg/m^3 at the west fenceline receptor or 1200 m from the facility's central source). The 2021 facility-specific AERMOD concentration was also the lowest of all three models with an output concentration of 0.46 µg/m^3 at the east fenceline receptor or 1300 m from the facility's central source. All maximum concentrations were observed directly at the fenceline receptors, however the 2019 and 2021 maximum concentrations for the facility-specific AERMOD run were observed at different locations of the receptors (west versus east respectively). This is likely due to the use of different meteorological datasets for the different years, as presented in the EPA MON RTR and TCEQ dispersion modeling guidelines. This difference in location was not observed in the TSCA Full-Screen model, likely because the meteorological dataset was based on Houston Hobby Airport data, which is considerably farther from the modeled facility than the nearby HRM-16 site.
Further highlighting the overly conservative output concentrations estimated by the proposed TSCA pre-screening methodology (IIOAC), a comparison with the TSCA full-screening methodology (simplified AERMOD) shows that the IIOAC-predicted output concentrations are about an order of magnitude greater than those predicted by a simplified AERMOD run (e.g. 10.75 µg/m^3 vs. 1.04 µg/m^3 for the 2019 TRI dataset). Although the IIOAC tool is built based on pre-run AERMOD scenarios, it is apparent that certain changes incorporated in the TSCA full-screen approach help make the model outputs more realistic and considerably less conservative, even though the input emission rates are the same (2019 TRI or 2021 TRI datasets). The major difference between both methods was the ability to choose a more representative meteorological dataset for the facility of choice (William P. Hobby airport (TX) instead of the pre-set IIOAC choice of Lake Charles, LA).

When comparing the TSCA full-screen methodology (simplified AERMOD) to the permit-style AERMOD run, it is important to note that major differences include the use of emission inventory rates (2020 NEI and NEI-off-year 2019 EPA modeling file emission rates), placement of source coordinates at actual emission points, use of a "denser" receptor grid, and the use of on-site meteorological data. With these differences in mind, the permit-style AERMOD runs for 2019 and 2021 provide output concentrations that are ~50% less than the TSCA full-screening approach. This applies for both modeling years, and for the various receptor points (maximum receptor point, HRM-16 or near-fenceline point, HRM-3, or offsite receptor point). While a true permit-style AERMOD run would also include building downwash from neighboring facilities, the setup in this report follows the dispersion modeling methodology used in the MON RTR (2020) docket[36] which excludes downwash effects.

1.4.3 Modeling study using predicted post-MON concentrations

On August 12th 2020, the EPA published its final rule on "National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review" in which the preamble mentions significant emission reduction of HAPs[38] including 1,3-butadiene. The preamble states the "sources of HAP emissions regulated by the MON include the following: process vents, storage tanks, transfer racks, equipment leaks, wastewater streams, and heat exchange systems." Furthermore, the EPA included supplemental attachments[39] in the docket that provide predicted post-control emission rates for all evaluated sources. The reductions were based on the facility location, type of source (process vent, storage tank, etc.), and the MON chemical in question. For the facility used in this modeling study, the EPA's predicted post-control emission rates were 3.9% less than the actual emission rates for fugitive/area sources. Thus, the modeling study (Boxes 1, 2, and 3 in Figure 2) was conducted again modifying the 2019 emission rates by the emission reductions predicted in the MON rule (3.9% for fugitive sources), while keeping all other parameters constant.

Table 7 provides the model study results for year 2019 data with predicted post-MON reductions applied. Note that the compliance dates for several changes (e.g. ethylene oxide provisions) in the 2020 MON Final Rule were effective upon publication of the final rule (August 12th 2020), while the compliance date for some changes (including replacement of maintenance startup and shutdown exemptions with the obligation to "comply at all times"; new requirements for multi-point flares, etc.) was 3 years from the publication of the final rule (i.e. August 12th 2023).

Note that in Table 7, the concentrations are provided in µg m^{-3} with corresponding ppb values provided in parentheses.

Table 7: Box 1 to Box 3 Model Study Results for Year 2019 (post-MON reduction)

Unit: µg/m^3 (ppb)	TSCA Pre-screening IIOAC Point | Area		TSCA Full-screening (Simplified AERMOD)	Permit-style (Facility-specific AERMOD)
Fenceline concentration (high-end)	4.37 (1.97)	6.13 (2.76)		
Community concentration (high-end)	1.22 (0.55)	0.42 (0.19)		
Model Maximum concentration			1.03 (0.46)	0.43 (0.19)
HRM-3 Receptor concentration			0.06 (0.03)	0.04 (0.02)
HRM-16 Receptor concentration			0.12 (0.05)	0.05 (0.02)

Given the small percentage difference in predicted emission rates for this facility's sources (3.9% for fugitive sources), the model study outputs are unsurprisingly like the 2019 model study results with no post-MON reductions applied. The same conclusions from the 2019 and 2021 model studies apply: the IIOAC tool provides the most conservative results, followed by the simplified AERMOD run, and the facility-specific AERMOD run.

1.4.4 Comments on predicted post-HON conditions

On April 25th 2023, the EPA published a proposed rule titled "New Source Performance Standards for the Synthetic Organic Chemical Manufacturing Industry and National Emission Standards for Hazardous Air Pollutants for the Synthetic Organic Chemical Manufacturing Industry (SOCMI) and Group I & II Polymers and Resins Industry (P&R)", hereby referred to as the proposed HON rule.[40] The preamble of the rule claims that there will be reduced emissions of various HAPs from improvements to flares, process vents, heat exchange systems, equipment leaks, wastewater systems, maintenance vents, storage tanks, and pressure relief devices (PRDs). Additionally, the proposed HON rule

[38] RTR for 2020 MON final rule preamble: https://www.federalregister.gov/d/2020-12776/p-456
[39] Attachment within rule docket documentation: https://downloads.regulations.gov/EPA-HQ-OAR-2018-0746-0189/attachment_1.xlsx
[40] Proposed HON rule webpage: https://www.federalregister.gov/documents/2023/04/25/2023-07188/new-source-performance-standards-for-the-synthetic-organic-chemical-manufacturing-industry-and

will include fenceline monitoring for facilities in the SOCMI and P&R I source categories that use, produce, store, or emit benzene, 1,3-butadiene, chloroprene, ethylene oxide, ethylene dichloride, or vinyl chloride.

Notably, while the TSCA pre-screening and full-screening outputs for the 2019, 2021, and post-MON 2019 studies result in concentrations greater than or close to the proposed HON rule action level (3 µg/m^3 for 1,3-butadiene), the permit-style (facility-specific) AERMOD simulations predict maximum concentrations that are lower (maximum annual average of 0.46 µg/m^3 for Year 2021).

The following table (Table 8) summarizes information on HON impacts from an operational perspective. For the facility that was modelled in the present analysis, the post-HON emission reductions of 1,3-butadiene are expected to be minor. This is since the test facility already meets TCEQ's HRVOC requirements for controls, monitoring/testing, recordkeeping, and reporting. Furthermore, all the flares on this site are already covered by other EPA regulations (i.e., refinery flare rule and ethylene MACT).

If another test facility is considered, one not already subject to HRVOC requirements, then an estimate of 1,3-butadiene emission reductions can be assumed from TCEQ documents[41]. The design of the HRVOC program was to achieve a 36% reduction in HRVOCs, specifically ethylene, propylene, 1,3-butadiene and butenes. This level of emission reduction can be reasonably assumed for each individual HRVOC.

Depending on the starting status for another test facility and the types of emission sources at the facility, 1,3-butadiene emission reductions could be up to 36%. However, for most facilities, existing MON and EMACT requirements likely would result in significantly smaller emission reductions.

Table 8: Summary of HON impacts on facility operations

Source Type	Proposed Change
Heat Exchange Systems	• Monitoring must be conducted using the Modified El Paso Method with a leak definition of 6.2 parts per million by volume (ppmv). • Quarterly monitoring preceded by an initial 6-month period where monitoring is conducted monthly. • Establishes a delay of repair action level of 62 ppmv. If this value is exceeded, delay of repair cannot be used beyond 30 days.
Storage Vessels	• Group 1 storage tank characteristics will change from 75 m^3 -151 m^3 and 13.9 kPa to 38 m^3 – 151 m^3 and 6.9 kPa. • Internal floating roof (IFR) tanks must be equipped with deck covers for certain fittings and controls for guide poles. If a blanket, purge, or sweep is used between the floating and fixed roof, it must be routed to control.
Process Vents	• Group 1 process vent characteristics will change to any process vent that emits greater than or equal to 1.0 pounds/hour (lb/hr) of total organic hazardous air pollutants (HAP)
Fenceline Monitoring	• Fenceline monitors must be deployed to measure fenceline concentrations of benzene, 1,3-butadiene, chloroprene, ethylene dichloride, ethylene oxide, and vinyl chloride if the site uses, produces, stores, or emits any of these compounds. • Must initiate root cause analysis and take corrective actions to reduce fugitive emissions if measured concentrations exceed the action level for any monitored pollutants.
Flares	• Flares used to comply with the emissions standard are subject to the requirements in 40 CFR Part 63, Subpart CC (Refinery MACT), with certain clarifications and exemptions.
Pressure Relief Devices (PRDs)	• For PRDs not routed to a control device, process, fuel gas system, or drain system, the following requirements will be added: – Install monitoring system to alert when a PRD release occurs. – Three redundant prevention measures must be implemented. – Conduct a root cause analysis and initiate appropriate corrective action in response to any PRD releases. • Limit number of PRD releases to one, two, or three releases in a three-year period depending on the cause of the release.
Bypass Lines	• A monitoring system capable of detecting when stream is diverted through a bypass must be installed; or

[41] https://www3.epa.gov/ttnchie1/conference/ei17/session6/thomas.pdf

	– Bypass lines must be secured in a closed position with car-seal or lock and key type mechanism.
Maintenance Activities	• Work practice standards for storage vessel degassing, storage vessel maintenance, and equipment opening will be added. • Exemptions for startup, shutdown, and malfunction (SSM) will be removed.
Pressure Vessels	• Pressure vessels greater than 204.9 kPa and without emissions to atmosphere are no longer excluded from the definition of storage vessel. • A definition for pressure vessels has been added. • Must conduct leak detection and repair (LDAR) monitoring initially and annually, with a leak definition of 500 ppm.
Surge Control Vessels and Bottom Receivers	• Any equipment with total organic HAP greater than 1.0 lb/hr would require control to 98%, 20 ppmv, or emissions must be routed to a flare meeting the new flare requirements.
Transfer Operations	• The exemption for transfer operations at greater than 204.9 kPa has been removed.

The final rule is expected in Spring 2024.

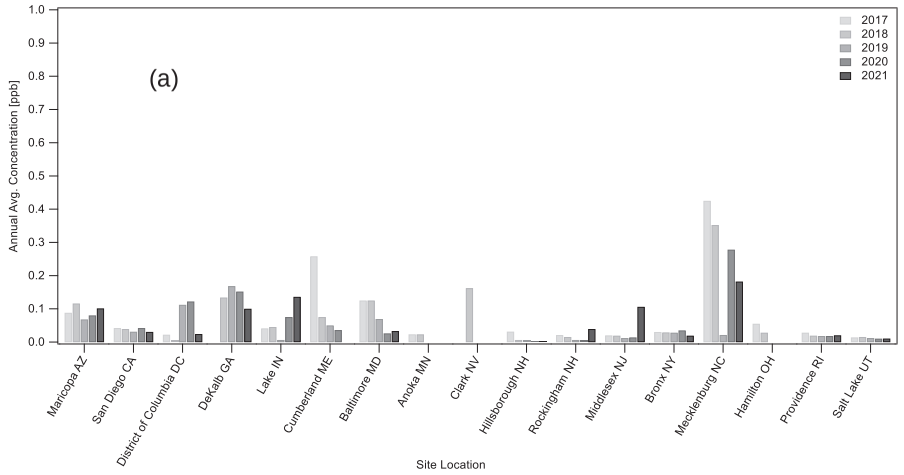
4. Ambient Air Monitoring

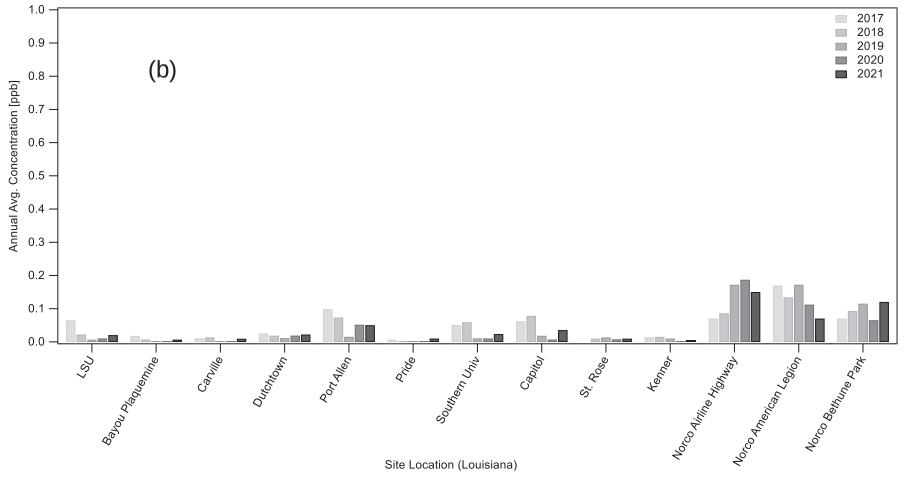
1.5 1,3-butadiene ambient air monitoring trends from 2017 to 2021

Since 1,3-butadiene has multiple sources and arises not only from manufacturing and/or use, monitoring data can more accurately represent air concentrations at which communities may be exposed. To put the air dispersion modeling study results from previous sections into context, ambient air concentrations of 1,3-butadiene measured at various sites with automated gas chromatography (auto-GC) measurements (owned/operated by EPA, LDEQ, and TCEQ) from years 2017 to 2021 were analyzed. Most sites that were selected for this data analysis are in the state of Texas. This data was chosen as the Texas air monitoring network is known to be one of the most extensive in the nation[42], with validated data that is available for public access[26].

Figure 6 provides annual average concentrations of 1,3-butadiene for (a) various nationwide sites, (b) sites in Louisiana, (c) sites in Texas (TCEQ Regions 4 and 12, i.e. Dallas/Fort Worth and Houston). The nationwide sites chosen are all air monitoring sites that collect autoGC data measuring various VOCs including 1,3-butadiene, and which have ambient air quality data publicly available through EPA's Air Quality System (AQS) website. The selected Texas and Louisiana sites are all air monitoring sites measuring 1,3-butadiene using an autoGC and which have publicly available air quality data available through the TCEQ website (TAMISweb) and LDEQ website[43] respectively. Since the TCEQ air monitoring network is one of the most expansive in the nation, we focus on air quality data from the cities of Houston and Dallas only. Site-to-site trends are generally consistent over the years of this analysis, and all annual average concentrations appear to be lower than 1 ppb (with the exception of one site in Texas in 2021, which experienced extreme weather conditions).

[42] TCEQ Ambient Air Monitoring webpage: https://www.tceq.texas.gov/airquality/monops
[43] https://www.deq.louisiana.gov/page/ambient-air-monitoring-data-reports


(a)
2017
2018
2019
2020
2021
Annual Avg. Concentration [ppb]
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Maricopa AZ
San Diego CA
District of Columbia DC
DeKalb GA
Lake IN
Cumberland ME
Baltimore MD
Anoka MN
Clark NV
Hillsborough NH
Rockingham NH
Middlesex NJ
Bronx NY
Mecklenburg NC
Hamilton OH
Providence RI
Salt Lake UT
Site Location


(b)
2017
2018
2019
2020
2021
Annual Avg. Concentration [ppb]
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
LSU
Bayou Plaquemine
Carville
Dutchtown
Port Allen
Pride
Southern Univ
Capitol
St. Rose
Kenner
Norco Airline Highway
Norco American Legion
Norco Bethune Park
Site Location (Louisiana)

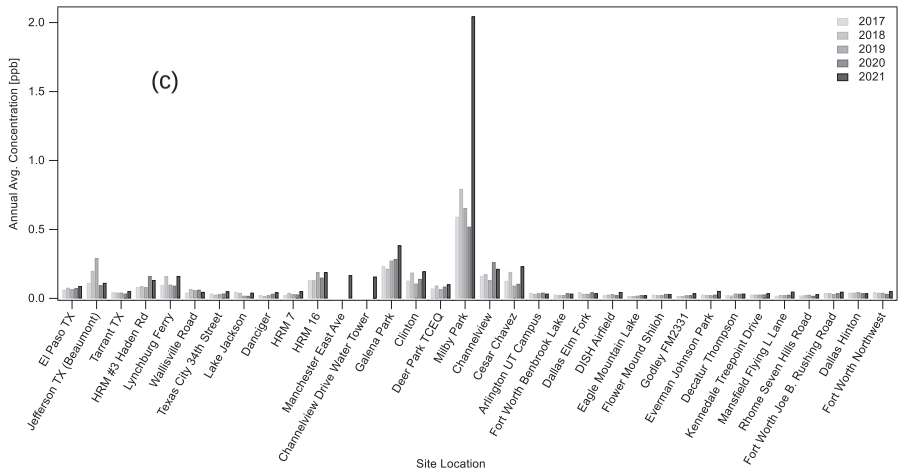


Figure 6: 1,3-butadiene annual average concentrations at (a) several EPA nationwide sites, (b) Louisiana sites, (c) Texas sites

Taking a closer look at Figure 6 (c), it appears that sites in Harris County, TX (TCEQ Region 12, sites from HRM#3 to Cesar Chavez) have slightly higher 1,3-butadiene concentrations compared to sites in Dallas, TX (TCEQ Region 4). A more detailed discussion on potential reasons for this is provided in Section **Error! Reference source not found.** of this report.

Table 9 presents the same 1,3-butadiene annual average concentrations as Figure 6 in a tabulated format. The rows highlighted in light green (HRM-3, HRM-16, and Milby Park) correspond to select sites with higher-than-average concentrations of 1,3-butadiene (compared to nationwide averages).

Table 9: Annual average 1,3-butadiene concentrations (ppb) at various nationwide air monitoring sites (2017-2021)

(TCEQ) Region	Site Name	Site Description	Annual Average 1,3-Butadiene Concentration [ppb]				
			2017	2018	2019	2020	2021
12	Site_22_3	HRM #3 Haden Rd	0.081	0.087	0.080	0.16	0.13
12	Site_23_2	Lynchburg Ferry	0.097	0.16	0.099	0.092	0.16
12	Site_24_1	Wallisville Road	0.042	0.067	0.058	0.062	0.047
12	Site_25_1	Texas City 34th Street	0.034	0.026	0.031	0.035	0.051
12	Site_26_1	Lake Jackson	0.047	0.040	0.019	0.018	0.041
12	Site_28_1	Danciger	0.024	0.016	0.022	0.033	0.044
12	Site_47_2	HRM 7	0.024	0.040	0.031	0.028	0.052
12	Site_48_1	HRM 16	0.13	0.13	0.18	0.15	0.23
12	Site_55_3	Manchester East Ave	–	–	–	–	0.17
12	Site_56_2	Channelview Drive Water Tower	–	–	–	–	0.16
12	Site_72_5	Galena Park	0.23	0.21	0.27	0.29	0.38
12	Site_A_2	Clinton	0.13	0.19	0.11	0.14	0.20
12	Site_H_1	Deer Park_TCEQ	0.071	0.093	0.065	0.085	0.10
12	Site_K_2	Milby Park	0.59	0.79	0.66	0.52	2.04
12	Site_R_2	Channelview	0.16	0.17	0.13	0.26	0.21
12	Site_V_1	Cesar Chavez	0.13	0.19	0.093	0.10	0.23
4	C1018_Site_2A_1	Arlington UT Campus	0.038	0.032	0.036	0.041	0.034
4	C1503_Site_2B_1	Fort Worth Benbrook Lake	0.028	0.023	0.024	0.037	0.034
4	C1505_Site_2C_1	Dallas Elm Fork	0.043	0.032	0.033	0.043	0.037
4	C1013_Site_2D_2	DISH Airfield	0.021	0.027	0.030	0.024	0.046
4	C75_Site_2E_2	Eagle Mountain Lake	0.016	0.016	0.019	0.023	0.022

4	C1007_Site_2F_2	Flower Mound Shiloh	0.026	0.023	0.023	0.032	0.031
4	C1501_Site_2G_1	Godley FM2331	0.016	0.017	0.021	0.023	0.036
4	C1009_Site_2J_2	Everman Johnson Park	0.027	0.023	0.022	0.027	0.054
4	C88_Site_2T_2	Decatur Thompson	0.021	0.020	0.034	0.033	0.034
4	C1062_Site_62_1	Kennedale Treepoint Drive	0.027	0.027	0.027	0.028	0.036
4	C1063_Site_63_1	Mansfield Flying L Lane	0.018	0.023	0.023	0.026	0.049
4	C1064_Site_64_1	Rhome Seven Hills Road	0.020	0.022	0.026	0.018	0.029
4	C1065_Site_65_1	Fort Worth Joe B. Rushing Road	0.037	0.037	0.031	0.037	0.048
4	C60_Site_E_3	Dallas Hinton	0.041	0.041	0.044	0.036	0.036
4	C13_Site_F_10	Fort Worth Northwest	0.043	0.040	0.040	0.032	0.053
National	4_13_4003	Maricopa AZ	0.088	0.12	0.07	0.08	0.10
National	6_73_1	San Diego CA	0.042	0.039	0.031	0.042	0.030
National	11_1_43	District of Columbia DC	0.022	0.0040	0.11	0.12	0.024
National	13_89_2/**3**	DeKalb GA	--	0.13	0.17	0.15	0.10
National	18_89_22/34/**35**/2008	Lake IN	0.041	0.045	0.006	0.075	0.14
National		Capitol LA	0.061	0.065	0.037	0.032	0.035
National		Dutchtown LA	0.031	0.018	0.024	0.028	0.026
National	23_5_29	Cumberland ME	0.26	0.075	0.050	0.036	
National	24_5_3001	Baltimore MD	0.12	0.12	0.069	0.026	0.033
National	27_3_1003	Anoka MN	0.023	0.023	--	--	--
National	32_3_540	Clark NV	--	0.16	--	--	--
National	33_11_5001	Hillsborough NH	0.031	0.0060	0.0035	0.00042	0.0027
National	33_15_18	Rockingham NH	0.021	0.015	0.0059	0.0041	0.039
National	34_23_11	Middlesex NJ	0.020	0.019	0.012	0.014	0.11
National	36_5_110	Bronx NY	0.030	0.029	0.028	0.035	0.019
National	37_119_41	Mecklenburg NC	0.42	0.35	0.021	0.28	0.18

National	39_61_47	Hamilton OH	0.055	0.028	--	--	--
National	44_7_22	Providence RI	0.028	0.019	0.018	0.018	0.020
National	48_113_69	Dallas TX	0.042	0.042	0.046	0.038	0.038
National	48_141_44	El Paso TX	0.063	0.077	0.066	0.073	0.089
National	48_245_1035	Jefferson TX (Beaumont)	0.11	0.20	0.29	0.094	0.11
National	48_439_1002	Tarrant TX	0.044	0.042	0.042	0.035	0.053
National	49_11_4	Salt Lake UT	0.014	0.015	0.012	0.010	0.010

Building on the discussion in Section 1.4.2 of this report, the annual average measured concentration of 1,3-butadiene for the year 2019 at the HRM-16 (near-fenceline) site was 0.18 ppb or 0.40 µg/m^3 which was considerably less than the TSCA pre-screening (annual average) model output of 4.84 ppb or 10.75 µg/m^3, less than TSCA full-screen model maximum output of 0.47 ppb or 1.04 µg/m^3, and of similar magnitude to the Facility-Specific AERMOD maximum concentration of 0.20 ppb or 0.44 µg/m^3. Note that the model outputs are the 95th percentile result for the TSCA pre-screening model (IIOAC) and the maximum concentration result for the TSCA full-screen model and Facility-Specific AERMOD. Additionally, the TSCA pre-screening model output discussed here is the concentration directly at the fenceline whereas the TSCA full-screen output and the ambient concentrations are measured at a nearby air monitoring site (HRM-16, 0.82 miles from modeled facility). These results highlight the conservative nature of the TSCA pre-screening approach which is not predictive of real ambient concentrations, where the suggested model predicts concentrations that are higher than those measured by air monitoring stations near the facility. The data from monitoring sites reflects aggregate exposures from multiple industrial sites and other sources, and is impacted by environmental and seasonal effects which are not necessarily captured in screening models. As such, it is expected that a realistic model would provide an output concentration of 1,3-butadiene that is considerably lower than the ambient annual average concentration which incorporates several (industrial and non-industrial) sources. In that regard, the Facility-Specific AERMOD, which is considered the best available science, provides more realistic predicted ambient concentrations, albeit still conservative, for this case-study facility. The Facility-Specific modeled concentration is considered conservative as model outputs are only based on modeling the sources in a single case-study facility, whereas measured concentrations are based on all industrial, and non-industrial (mobile and area) sources in the monitoring location.

A similar analysis for the year 2021 shows that the measured annual average concentration of 1,3-butadiene at the HRM-16 (near-fenceline) site was 0.23 ppb or 0.51 µg/m^3 which was less than the TSCA pre-screening model output of 4.36 ppb or 9.69 µg/m^3 and the TSCA full-screen model maximum of 0.33 ppb or 0.74 µg/m^3, and of similar magnitude to the Facility-Specific AERMOD which had model maximum concentrations of 0.21 ppb or 0.46 µg/m^3. Here we note again that the Facility-Specific model is still considered conservative as model outputs are only based on the sources within this case-study facility, whereas measured concentrations are based on all industrial and non-industrial sources in the monitoring location.

An EPA Memorandum titled “Guidance on the Use of Models and Other Analyses for Demonstrating Attainment of Air Quality Goals for Ozone, PM2.5, and Regional Haze”[44] discusses how to compare model outputs to observed (measurement) data. In that work, cases with factors of 2 under- and over-prediction are considered to meet “performance criteria”, i.e. the model results are acceptable when compared to measurement data. The memorandum suggests that less abundant species should have less stringent proposed “performance goals” (close to best achievable results) and “performance criteria” (acceptable results). Although no qualitative benchmark is provided for less abundant species (such as 1,3-butadiene), the memorandum recommends allowing for larger bias and error when the ambient concentration of any species falls below 2 µg m^{-3}, as the model’s ability to make accurate predictions decreases at lower concentrations. Additionally, the EPA recommends against the use of such benchmarks in a pass/fail mode but only as

[44] https://www3.epa.gov/ttn/naaqs/aqmguide/collection/cp2_old/20070418_page_guidance_using_models.pdf

a means of assessing general confidence in data, alongside other qualitative or quantitative procedures to assess overall model performance (e.g. the discussion of Positive Matrix Factorization in the forthcoming section of this report).

Figure 7 presents historical trends of 1,3-butadiene based on work from Hendler et al. (2010)[45] (shown in grey) compared to data analysis conducted as part of this report (shown in red). The graphics show that for almost all Houston sites (with minor exceptions), concentrations of 1,3-butadiene have substantially reduced since 1995-2009.

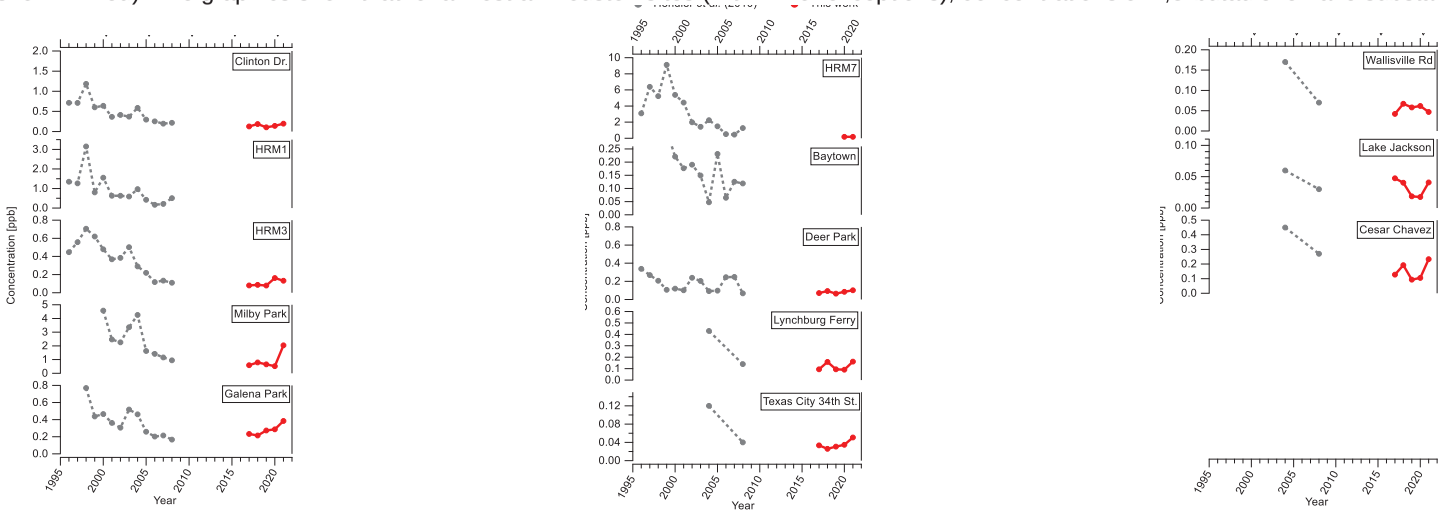


Figure 7: Historical trends of 1,3-butadiene concentrations at various Region 12 sites (1995 - 2023 YTD)

[45] Hendler AH, Goodmanson Bunch AT, Crow WL. Long-term trends in ambient air 1,3-butadiene levels in Houston, Texas. Environ Sci Technol. 2010 Oct 1;44(19):7383-90.

A similar trend is seen in Figure 8 where 1,3-butadiene emissions reported to EPA's TRI have fallen since 2009 (black trace, left axis). A comparison of ambient annual average concentrations from 2017-2021 (red traces, right axis) show similar trends to the TRI-reported values, especially for years 2017-2020. The zip code 77017 was chosen for this analysis as that is where the TCEQ's Milby Park and Cesar Chavez air monitoring sites are located. The uptick in Milby Park concentrations for the year 2021 may be related to severe weather events in 2021 namely the winter storm Uri that affected several cities in Texas including Houston (where Milby Park and Cesar Chavez are located). Not shown in Figure 7 is the Milby Park annual average concentration in 2022 (0.713 ppb) which was similar to the annual average concentration in 2020 (0.519), which further supports the idea that the 2021 annual average was an anomalously high value due to extreme weather conditions.

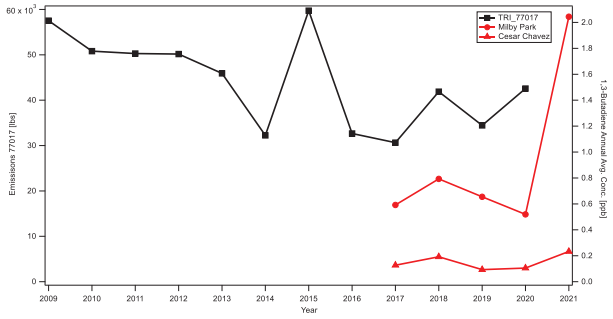


Figure 8: Comparison of 2009-2020 Toxic Release Inventory data within zip code 77017 (left) to 2017-2021 ambient monitoring data (right)

5. Conclusions

In this work, we assessed the EPA's TSCA Screening Level Approach (EPA Document# EPA-744-D-22-001) by examining the Pre-Screening and Full-Screening methodologies proposed. We chose a case study facility that has reported 1,3-butadiene emissions, and which was previously evaluated by the EPA as part of the Office of Air's Residual Risk Assessment for the MON in support of the 2020 Risk and Technology Review (Docket EPA-HQ-OAR-2018-0746).

We compared the Pre-Screening and Full-Screening models to an air dispersion model that is set up following the example provided in the 2020 MON RTR using emissions data from 2019 and 2021. The modeled maximum concentrations for both years showed similar trends where TSCA Pre-screening (IIOAC) outputs consistently had the highest values (10.75 $\mu g/m^3$ and 9.69 $\mu g/m^3$ for years 2019 and 2021 respectively), followed by the TSCA Full-Screening AERMOD (1.04 $\mu g/m^3$ and 0.74 $\mu g/m^3$), with the MON-RTR or "permit-style" AERMOD run producing the lowest output concentrations (0.44 $\mu g/m^3$ and 0.46 $\mu g/m^3$).

The modeling study highlights the conservative results from the TSCA Screening Level Approach methodologies, where the concentrations from the Pre-screening stage are an order of magnitude greater than the Full-screening stage, and the Full-screening stage concentrations are almost twice as high as concentrations from the MON RTR-based AERMOD run. Examining the modeled concentrations at various receptors extending from near-fenceline to ~5 miles away showed that **concentrations dropped considerably as distance from the facility increased**. The facility-specific AERMOD following the EPA's 2020 MON RTR methodology, which is considered the best available science, produced the most predictive (albeit still conservative) concentrations of all three models, because it utilized the most specific multi-variable inputs.

To put the air dispersion modeling studies into context, ambient air concentrations of 1,3-butadiene measured at various nationwide sites with automated gas chromatography (auto-GC) measurements from years 2017 to 2021 were analyzed and all concentrations (with the exception of one Texas site in 2021) were found to be below 1 ppb.

This work used the 1,3-butadiene-emitting case study facility to highlight the overly conservative nature of the methodologies proposed in the TSCA Screening Level Approach. Using facility data and guidelines available in the MON RTR final rule published by the EPA's Office of Air and a more refined air dispersion model run produced modeled concentrations that are more realistic, and more closely match with ambient measurements. Thus, in keeping with EPA's commitment to leverage existing data and resources, we encourage referral to the methodology followed in the EPA's MON RTR docket to provide refinement to the methodologies suggested in the TSCA Screening Level Approach.

Appendix A

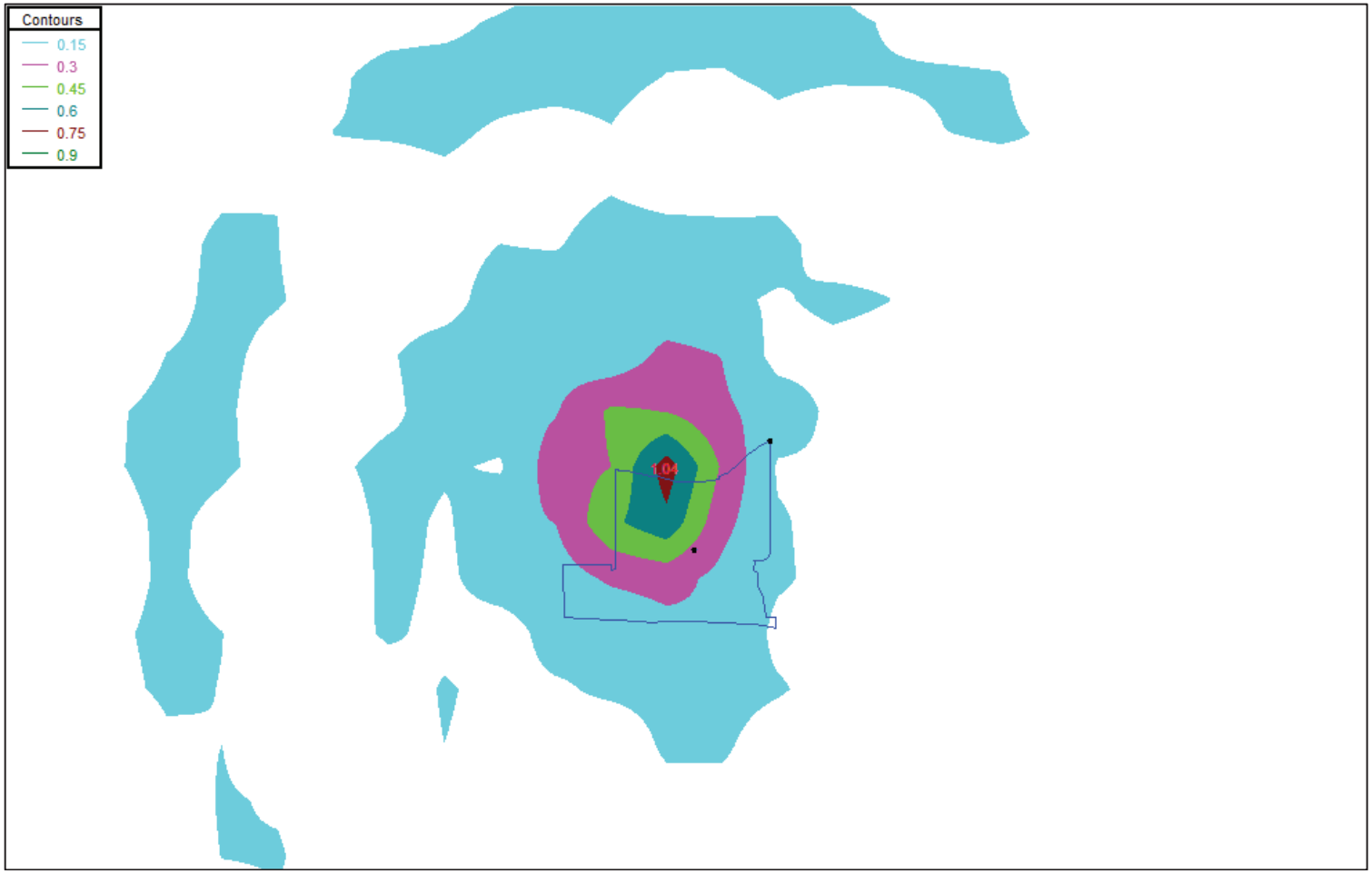


Figure A- 1 AERMOD Output Concentrations (µg m^{-3}) Contour Plot for TSCA Full Screen model for Year 2019

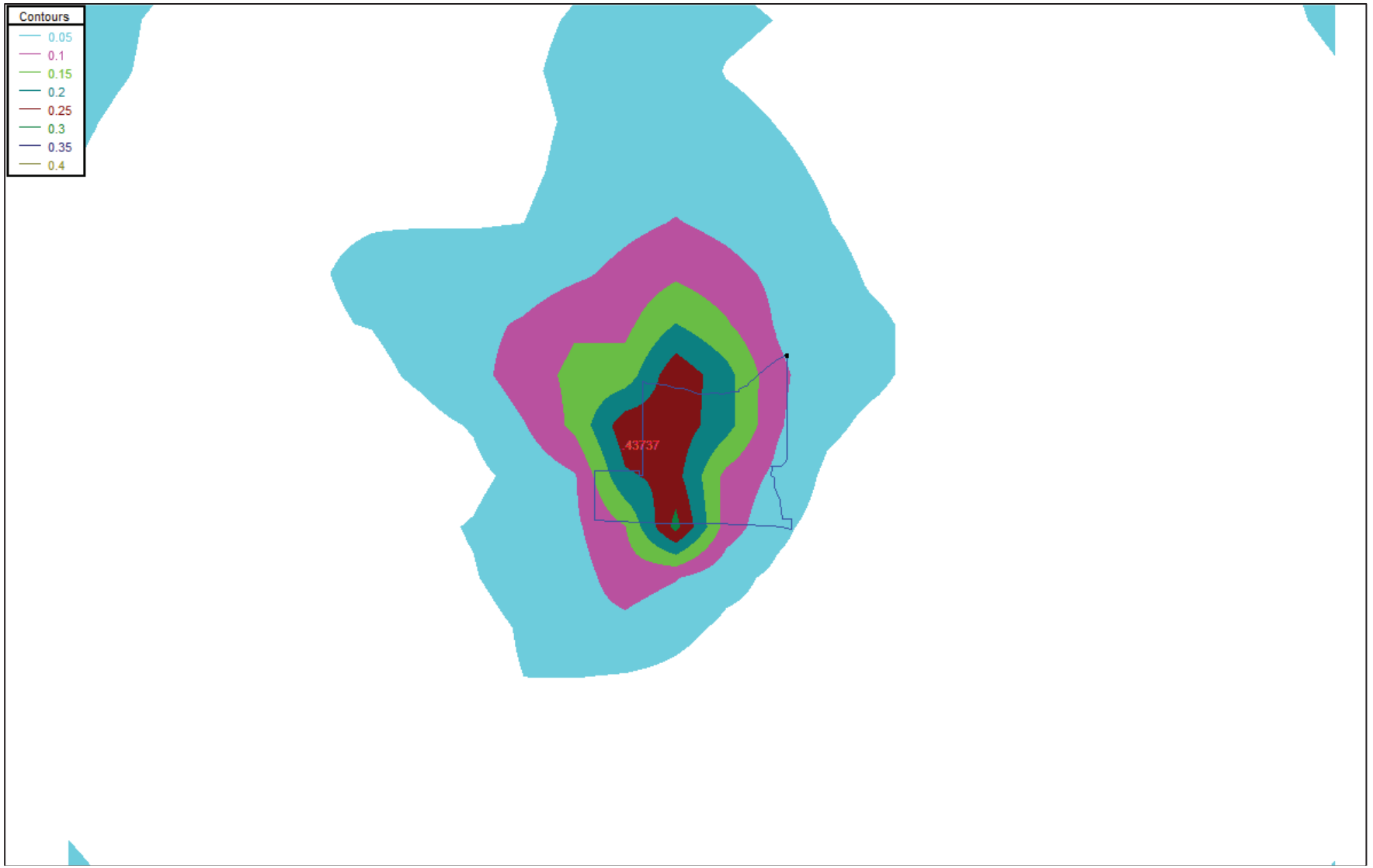


Figure A- 2 AERMOD Output Concentrations (µg m^{-3}) Contour Plot for Permit-style model for Year 2019

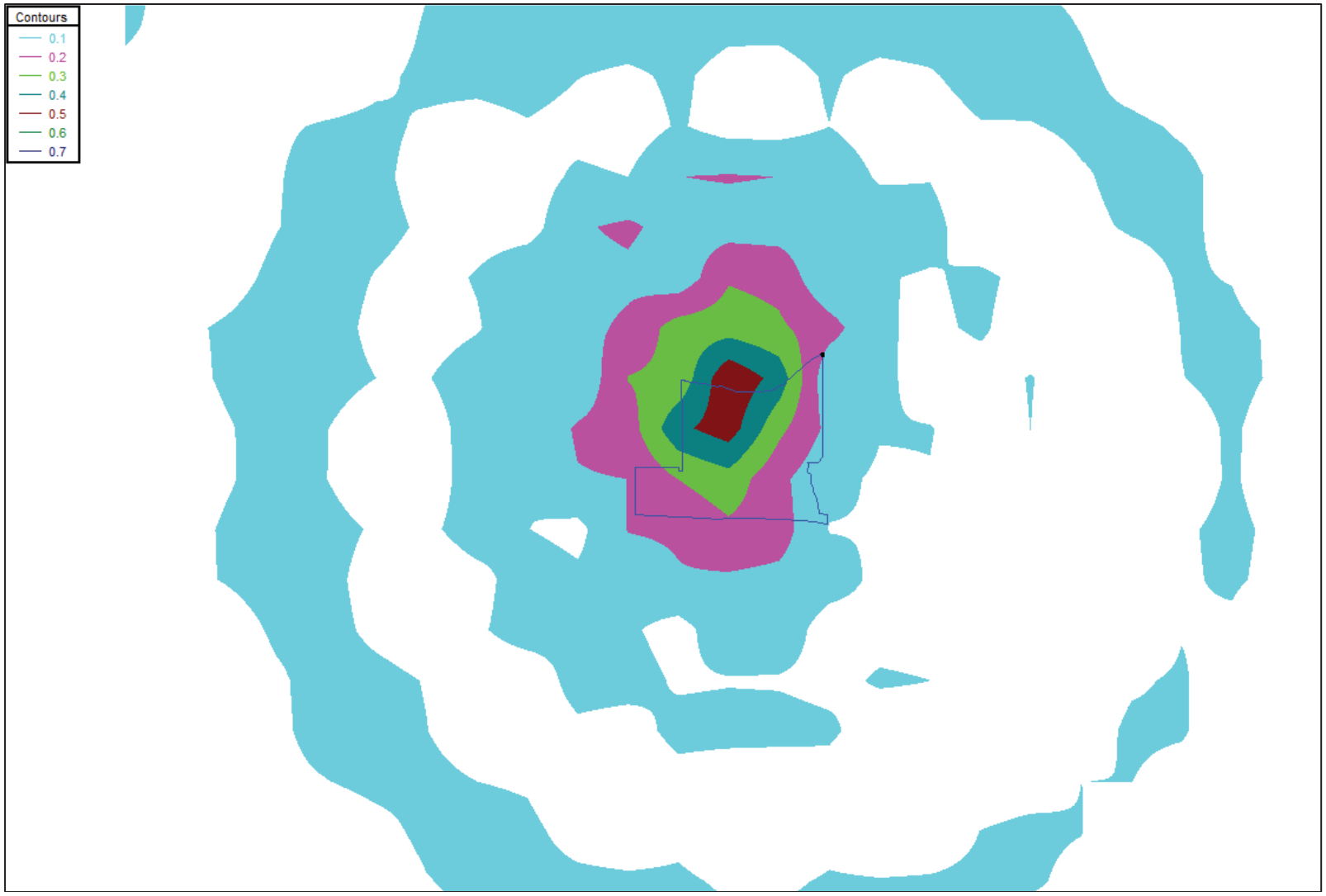


Figure A- 3 AERMOD Output Concentrations (µg m^{-3}) Contour Plot for TSCA Full Screen model for Year 2021

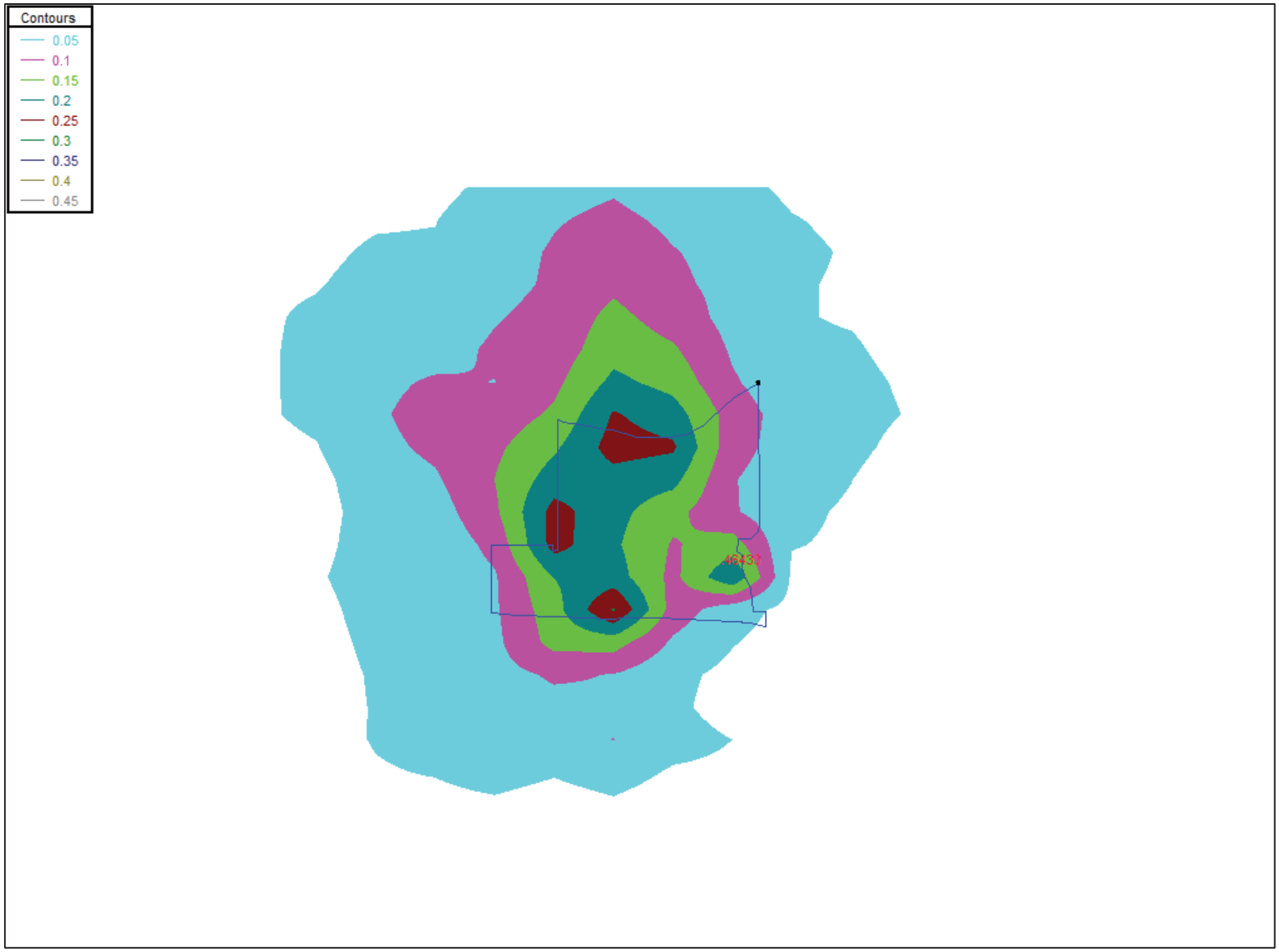


Figure A- 4 AERMOD Output Concentrations (µg m^{-3}) Contour Plot for Permit-style model for Year 2021

Residual Butadiene in BD-derived polymers and resins – Summary of the evidence

A non-systematic literature search was carried out to identify references that report measurements of residual 1,3-Butadiene (1,3-BD) in Butadiene-derived polymers and resins or assessed the potential migration of residual 1,3-BD from such polymers and resins. The following paragraphs summarize theoretical considerations and references and table 1 contains the reported values found in the previous 20 years of literature, while Appendix 1 provides an annotated bibliography. Appendix 2 provides links to studies that have assessed migration of additives or monomers from butadiene-derived polymers or resins, but do not report any measured butadiene, which has consistently been identified as the monomer with the lowest presence in the resins (compared to the other components).

Residual 1,3-BD in BD-derived resins and polymers

Since 1,3-BD is part of the building blocks for many plastics and resins (i.e., Styrene-Butadiene Rubber (SBR), Acrylonitrile-butadiene-styrene (ABS), etc.), it is expected that residual monomers in plastic will always be present to a certain extent (Ministry of Environment and Food Denmark, 2019).

Since butadiene has a low boiling point (-4.5°C) and thus is gas at room temperature, it can be expected based on theoretical considerations that any bioavailable residues of this monomer will easily evaporate from the polymer or during the high moulding process temperatures unless the residues are encapsulated in the polymer.

A good example is the heating of the plastic for calendaring/extrusion or mixing, all the way to vulcanization of SBR. These processes will lead to the volatilization of part or all (in the case of vulcanization, as demonstrated by EPA, 2017) the residual BD in the resins. Through heating, the solubility of most substances increases which will counteract a possible degassing of monomers with low boiling point and/or high vapor pressure. From theoretical considerations based on reaction kinetics it can be expected that there will be a correlation between process type and removal of residual monomers. (Ministry of Environment and Food Denmark, 2019).

Table 1 summarizes the reported concentrations measured and reported in public literature. An example are vendor specifications for Styrene Butadiene Rubber Copolymer (Food) with a maximum concentration of 0.5 mg/kg of 1,3-BD in the gum.

Several unpublished studies were identified that assessed residual levels of BD monomer in materials. The results of an unpublished survey conducted in 2020 with the manufacturers of synthetic rubber in the USA indicate that BD monomer levels were below the limit of detection (Table 2a,b). Similarly, the International Institute of Styrene Butadiene Rubber Producers shared data on residual butadiene in these rubbers, as reported by the Association of Petrochemical Industry of Japan (IISRP, 2020)

An unpublished study from 2001 measured the levels of BD monomer in four different ABS plastic samples, yielding a single detection that occurred at the detection limit (1 mg/kg; Table 3). A more recent survey of two different ABS plastics that contained BD monomer levels with mean concentrations ranging from 0.68±0.71 to 2.1±1.5 mg/kg (Table 3).

Potential for migration of 1,3-BD from plastics or resins

Theoretical considerations

The solubility of monomers in the polymer and the affinity of the monomers (i.e. tendency to bond by electrostatic forces) for the polymer are in general so high that as a rule, the monomers are difficult to force out. The rule of thumb is that the monomer is the best solvent for a given polymer. Therefore, it

cannot be expected that the residual monomers disappear completely with time, but stay in the matrix (i.e., limited to no bioavailability). However, this does not mean that the content of the residual monomers increases over time. Like for all chemical processes, a phase equilibrium will occur. (Ministry of Environment and Food Denmark, 2019).

The migration rate of organic chemical substances is size dependent. Small molecules, (e.g. monomers and residual solvents), with low boiling points, will migrate fast. In fact, some monomers e.g. formaldehyde, vinyl chloride, ethylene and butadiene have a tendency to migrate quickly even at ambient temperatures (Hahladakis et al (2018), Hansen et al, (2013)). Migration potential is impacted by a wide range of parameters, such as initial concentration of the monomer in the plastic, the thickness of the plastic material, the crystallinity of the plastic and the surface structure of the plastic have all a complex influence on the rate of migration (Hansen et al., 2013). Residual monomers in plastic will be in a phase equilibrium with the atmosphere and the plastic in which they are dissolved (Ministry of Environment and Food Denmark, 2019). It is important to note that addition of additives to plastic will influence the diffusion coefficient and thus the amount which migrates from the plastic as well as the migration rate (Genualdi et al., 2014). From a purely theoretical point of view, it must therefore be expected that the migration from solid plastic products, such as ABS will be very slow. (Ministry of Environment and Food Denmark, 2019).

Seen from a theoretical point of view, the following conditions regarding residual monomers in plastic and migration of residual monomers from plastic apply:

• The actual production process of the polymer is significant for the content of residual monomers. It is possible to reduce the content of residual monomers in the polymer by controlling the process conditions and use subsequent processes which may reduce the monomer content but there will always be a certain amount of residual monomer left in the polymer.

• The production method of articles (for instance injection moulding versus blown film) may be important for the content of residual monomers in the polymer.

• The migration of residual monomers from the polymer follows in theory Fick's Law, i.e. the migration depends on among other things the type of plastic (initial concentration), time, temperature, thickness of material and exposure for example for liquids.

• The migration will decrease with time as the concentration of the monomer in the plastic decreases and as an equilibrium between monomer content in the plastic and monomer content in the migration medium will occur.

• The migration may be expected to be largest to the medium/liquid in which the monomer is easily soluble (not the case for 1,3-BD, as it has low water solubility)

Summary of data regarding migration from plastic

Based on the low water solubility of 1,3-BD, it is expected that migration to aqueous agents will be low, while there is potential that higher migration is predicted for fatty food tests (since ethanol would be a likely simulant). Nevertheless, the few studies identified that report detections of 1,3-BD in oil, margarine, potato salad, cottage cheese, and yogurt describe concentrations ranging from <0.2 to 9 ng/g (ppb) ATSDR Tox Profile for 1,3-Butadiene (2012)

Table 1 also summarizes the little information about migration of the residual monomer butadiene that was found. Whether this is due to the fact that the content of the residual monomer butadiene is normally identified in small amounts (mostly < 1.7 mg/kg, maximum measurement 5.3 mg/kg) is unknown. However, this is the argument which Abe et al. (2013) state for not measuring the migration of butadiene from the toys they examined. Only data from one of the European toy producers (TIE,

2018) show that all the measurements (20 in total) are below the detection limit. (Ministry of Environment and Food Denmark, 2019).

In an unpublished study, the migration of BD monomer from four samples of ABS plastic was assessed using three different food simulants (3% acetic acid, 10% ethanol, olive oil). Migration was assessed using the following test conditions: 2 hours at 70 degrees C, 2 days at 40 degrees C, and 10 days at 20 degrees C. For all samples and test conditions except for 1, the levels of BD monomer were below the limit of detection (10 ug/kg simulant; Table 4). A single detection was report for one sample (ABS 4) and test condition and simulant (2 days, 40 degrees C, in olive oil) just slightly above the detection limit (12 ug/kg simulant).

Table 1. Summary of Published Literature on the Residual Content and Migration of 1,3-BD Monomer from Polymer Materials

Reference	Year	Material	Residual content (ug/g)	Migration to water (ng/ml)	Migration to air (ug/m^3)	Migration to food (ug/g)
Determination of Residual 1,3-Butadiene in Synthetic Resins containing Butadiene	1981	PBD	ND (< 1 ppm)	--	--	--
		ABS	ND (< 1 ppm)	--	--	--
Single ion monitoring of butadiene in plastics and foods by coupled mass spectrometry-automatic headspace gas chromatography	1984	ABS	<0.005 - 0.31			ND (< 0.0002) in margarine
Analysis of Acrylonitrile, 1,3-Butadiene, and Related Compounds in Acrylonitrile-Butadiene-Styrene Copolymers for Kitchen Utensils and Children's Toys by Headspace Gas Chromatography/Mass Spectrometry	2010	ABS	0.06–1.58	--	--	--
		AS	ND	--	--	--
		PS	0.01 - 0.08	--	--	--
Migration study of 1,3-butadiene in eye-drop solutions	2012	?	--	0 - 0.52 (after 12 months at 40C)	--	--
Analysis of trace residual 1,3-butadiene in poly(acrylonitrile-co-butadiene-co-styrene)	2012	ABS	0.002 - 0.003	--	--	--
Volatile Substances in Polymer Toys Made from Butadiene and Styrene	2013	ABS	0.04 - 5.3 (mean 0.78)	3 - 40	--	--
		thermoplastic elast.	<0.1	ND	--	--
		rubber toys (SBR)	< 0.1	ND	--	--
Survey of volatile substances in kitchen utensils made from acrylonitrile–butadiene–styrene and acrylonitrile–styrene resin in Japan	2014	ABS	0.06 - 1.7	ND	--	--
		AS	ND	ND	--	--
Toy Industries of Europe (TIE) (as reported in Survey of monomers in toy materials	2018	ABS	<0.01 - 5 (mean 0.29)	<0.01		
Survey and investigation of migration of monomers in toy materials	2019	ABS	0.23 - 1.55	<0.01	--	--
		SBC	<0.1 - 0.2	<0.01	--	--
Synthetic Turf Field Recycled Tire Crumb Rubber Research Under the Federal Research Action Plan. Final Report Part 1 – Tire Crumb Rubber Characterization Volume 1	2019	SBR recycled	--	--	--	--
		SBR turf field	--	--	--	--
Determination of 1,3-Butadiene Migrated from Butadiene-Based Polymers to Air and Water Using Sorbent Tubes and Purge-and-Trap	2021	ABS	--	ND	ND	--
		SBR	--	0.044±0.003	0.91±0.09	--
Styrene Butadiene Rubber Copolymer (Food)	2023	SBR	0.5 (maximum spec)	--	--	--

Table 2a. Unpublished Data on Residual BD Monomer in SBR (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

Table 2b. Unpublished Data from the Association of Petrochemical Industry of Japan (IISRP, 2020)

	Product Category	Product Detail (Commercial Name, sub-category, etc.)	Evaluation of Analysis		
			Residual BD	unit (ppm/%)	Method, Detection limit, Remarks
1	ESBR		N.D.	ppm	ISO17052 compatible, Lower limit of Detection:50ppm
2	SSBR		N.D.	ppm	ISO17052 compatible, Lower limit of Detection:50ppm
3	SSBR		N.D.	ppm	GC/MS Method Quantitation Limit: 1ppm
4	SSBR		N.D.	ppm	GC-FID Method Quantitation Limit: 10ppm
5	NBR		N.D.	ppm	ISO17052 compatible, Lower limit of Detection:50ppm
6	BR		N.D.	ppm	ISO17052 compatible or GC/MS Method, Lower limit of Detection:1ppm
7	SBS		N.D.	ppb	ISO17052 compatible, Quantitation Limit:4ppb
8	SEBS		N.D.	ppb	ISO17052 compatible, Quantitation Limit:10ppb
9	SEBS		N.D.	ppb	GC/MS Method Quantitation Limit: 1ppm

Table 3. Unpublished Data on Residual BD Monomer in ABS Plastic

				Residual BD (mg/kg)			
Year of analysis	**Sample**	**Analytical Method**	**DF**	**Minimum**	**Maximum**	**Mean**	**SD**
2001	ABS 1	GCMS	0/1	--	--	<1	--
2001	ABS 2	GCMS	0/1	--	--	<1	--
2001	ABS 3	GCMS	0/1	--	--	<1	--
2001	ABS 4	GCMS	1/1	--	--	1	--
2020-2023	ABS 5	Not specified	53/56	0.2	3.15	0.68	0.71
2020-2023	ABS 6	Not specified	595/595	0.1	10.4	2.1	1.5

Table 4. Unpublished Data for Migration of BD Monomer from ABS Plastic

Sample (residual BD, mg/kg)	**Simulant**	**Test Exposure (repeat use)**	**BD migration (ug/kg simulant)**		
			2 hours, 70 °C	**2 days, 40 °C**	**10 days, 20 °C**
ABS 1 (<1 mg/kg)	3% acetic acid	1st	ND*	ND	--
	10% ethanol		ND	ND	--
	olive oil		ND	ND	--
	3% acetic acid	3rd	ND	ND	--
	10% ethanol		ND	ND	--
	olive oil		ND	ND	--
ABS 2 (<1 mg/kg)	3% acetic acid	1st	--	--	ND
	10% ethanol		--	--	ND
	olive oil		--	--	ND
ABS 3 (<1 mg/kg)	3% acetic acid	1st	ND	ND	--
	10% ethanol		ND	ND	--
	olive oil		ND	ND	--
	3% acetic acid	3rd	ND	ND	--
	10% ethanol		ND	ND	--
	olive oil		ND	ND	--
ABS 4 (1 mg/kg)	3% acetic acid	1st	ND	ND	--
	10% ethanol		ND	ND	--
	olive oil		ND	12	--
	3% acetic acid	3rd	ND	ND	--
	10% ethanol		ND	ND	--
	olive oil		ND	ND	--

*GCMS Detection limit = 10 ug/kg simulant

Appendix 1:
Annotated summary of references reporting residual content or migration of BD from polymers

Old references already summarized in ATSDR Tox Profile for 1,3-Butadiene (2012)
1,3-Butadiene is used to manufacture synthetic rubber and plastics that are frequently used for food packaging. Because residual 1,3-butadiene may be present in the polymers used to make the containers, both the packaging and the food contained therein have been analyzed. In one study, 1,3-butadiene at a concentration of 8–9 ng/g (ppb) was detected in three of three brands of olive oil packaged in 1,3-butadiene rubber-modified acrylonitrile-acrylic bottles (McNeal and Breder 1987). Analysis of the bottles themselves found 1,3-butadiene residues as high as 6,600 ng/g (ppb). Soft-plastic packaging tubs used as containers for potato salad, cottage cheese, and yogurt had residual 1,3-butadiene levels in the range of 21–1,700 ng/g (ppb). However, no 1,3-butadiene was detected in any of the food packed in these containers (detection limit 1 ppb). Chewing gum made with a 1,3-butadiene rubber base did not show residual traces of this diene (McNeal and Breder 1987). Soft-plastic margarine tubs from five major name brands in the United Kingdom contained 1,3-butadiene residues ranging from 5 to 310 µg/kg (ppb), but none of the monomer was detected in the margarine samples themselves (detection limit 0.2 µg/kg) (Startin and Gilbert 1984). The authors concluded that migration of the 1,3-butadiene monomer from plastic packaging to food is unlikely to present a problem. Residual levels of 1,3-butadiene in food containers are closely regulated by the Food and Drug Administration. Pellizzari et al. (1995) measured 0.1 mg of 1,3-butadiene in rapeseed oil emissions during 20 minutes of heating the oil in a wok at 260 °C. The presence of 1,3-butadiene was attributed to the pyrolytic decomposition of unsaturated fatty acids in the oil.

Determination of Residual 1,3-Butadiene in Synthetic Resins containing Butadiene (Tan and Okada, 1981)
Samples of household wrapping film, ABS sheets, and kitchen utensils such as chopsticks, Ladles, graters, and lunch trays were analyzed for residual monomers. The reported concentrations of 1,3-BD were consistently below limit of detection (1 ppm)

Single ion monitoring of butadiene in plastics and foods by coupled mass spectrometry-automatic headspace gas chromatography (Startin and Gilbert, 1984)
The authors analyzed tubs of margarine and their contents to determine the potential migration of butadiene from ABS into foodstuff. Levels of butadiene in the ABS Plastics ranged from < 0.005 to 0.31 mg/kg and for the soft margarines were not detectable at a detection limit of 0.0002 mg/kg. The authors conclude that the absence of butadiene in the margarine suggests that this monomer is unlikely to present a problem through migration into foods.

Human exposures to monomers resulting from consumer contact with polymers (Leber, 2001)
A survey of all food-contact sources of butadiene monomer indicates negligible risks to consumers. The many worse-case assumptions that are used in surveys and analyses that estimate monomer exposures derived from polymers in contact with food provide assurances that these consumer products do not contribute in a significant manner to human health concerns.

Summary Risk Assessment Report (European Union JRC, 2002)
The only available measured data for the presence of monomer in indoor air suggest that indoor levels are generally below 2.2 µg/m3 (equivalent to 0.001 ppm), giving rise to an estimated daily dose of 5E-4

mg/kg/day for an adult or 7E-4 mg/kg/day for a toddler. The predicted reasonable worst-case oral dose of 1,3-butadiene as a result of leaching from packaging into foodstuffs is about 2.1E-4 mg/kg/day for an adult and 1.2E-3 mg/kg/day for a toddler. The combined exposure from indoor air and leaching from packaging into foodstuffs amounts to a predicted reasonable worst-case dose of 7E-4 mg/kg/day for an adult and 1.9E-3 mg/kg/day for a toddler.

Analysis of Acrylonitrile, 1,3-Butadiene, and Related Compounds in Acrylonitrile-Butadiene-Styrene Copolymers for Kitchen Utensils and Children's Toys by Headspace Gas Chromatography/Mass Spectrometry (Ohno, 2010)
Twenty-two samples made from ABS copolymer (13 kitchen utensils and nine children's toys). AS copolymers (5 kitchen utensils), PS (3 kitchen utensils and 2 food containers), and seven NBR gloves
In ABS copolymers, 1,3-BD was detected at 0.06–1.58 ug/g in all samples. The levels in children's toys were confirmed to be identical to those in kitchen utensils. 1,3-BD was not detected in AS copolymers,. In PS samples, 1,3-BD was detected at low levels compared with the ABS copolymers (levels were 0.01 and 0.08 ug/g).

Analysis of trace residual 1,3-butadiene in poly(acrylonitrile-co-butadiene-co-styrene) (Choi and Kim, 2012)

Residual 1,3-butadiene extracted from ABS pellets with toluene and N,N-dimethylacetamide was analyzed using GC-FID. ABS with the acrylonitrile, 1,3-butadiene, and styrene contents of 25, 17, and 58 wt%, respectively was used. The solvent extraction with toluene and N,N-dimethylacetamide was found to be much more efficient than the direct thermal desorption. The concentrations of 1,3- butadiene extracted with toluene and N,N-dimethylacetamide were about 3 and 2 ppb, respectively.

Migration study of 1,3-butadiene in eye-drop solutions (Pistos, 2012)
After 12 months of storage, all eight eye-drop solutions were negative for the migration of 1,3-BD after storage at 2–8°C. At room temperature, 1,3-BD appears to initiate the migration into one of the eye-drop solutions after 7 months of storage and increases almost linearly up to 12 months. At the same formulation, the migration seemed to be affected significantly by the temperature at 40°C after 4 months of storage and seemed to follow a linear increase up to 8 months.

Volatile Substances in Polymer Toys Made from Butadiene and Styrene (Abe, 2013)
The authors reported residual levels and migration behavior of volatile substances for acrylonitrile-butadiene-styrene copolymer (ABS) toys, thermoplastic elastomer toys, and rubber toys made from 1,3-butadiene and styrene found on the Japanese market. They analyzed 73 toy samples comprising 59 ABS toys, 12 thermoplastic elastomer toys, and 2 styrene-butadiene rubber toys.
The maximum residual level of 1,3-butadiene was 5.3 µg/g, which is much lower than the EU limit of 0.1%. Furthermore, some volatile substances migrated from ABS toys into water in amounts of 3 - 40 ng/mL. Thermoplastic elastomer toys and rubber toys contained these volatile substances at significantly lower levels than ABS toys.
They selected the toys with the highest concentration of residual VOCs to test migration into water (as surrogate of saliva). The authors did not detect any migration of 1,3-BD.

Survey of volatile substances in kitchen utensils made from acrylonitrile–butadiene–styrene and acrylonitrile–styrene resin in Japan.(Abe, 2014)
They looked at residual (not migrated) concentrations of 1,3-BD and other substances in 30 kitchen utensils made from acrylonitrile–butadiene–styrene resin (ABS) and acrylonitrile–styrene resin (AS) such

as slicers, picks, cups, and lunch boxes. The residual levels of 1,3-butadiene ranged from 0.06 to 1.7ug/g in ABS, where only three of 15 ABS samples exceeded the regulatory limit for this compound as established by the European Union (1 ug/g = 1 ppm). The residual levels of 1,3-butadiene in 15 of the AS sables were below the limit of quantitation (0.025 ug/g).

Monomers - Proposed requirements for Appendix C of the Toy Safety Directive (ANEC - The European consumer voice in standardization, 2018)
Corroborates the limit of 1 mg/Kg residual 1,3-BD as acceptable for toys and consumer uses. This limit is also applied to foodstuff (EFSA)

Toy Industries of Europe (2018) (as reported in Survey and investigation of migration of monomers in toy materials)
This report summarizes analyses of the content of residual monomers in ABS material used for toys (examined via the standards in the EN 1313018 series). The content of 1,3-BD was measured to:
• 9 samples did not contain butadiene (detection limit 0.01 mg/kg)
• 7 samples contained between 0.06 and 0.76 mg butadiene/kg (average value 0.29 mg/kg)
• 5 samples contained between 1 and 5 mg/kg
They also examined migration (via the standards in EN 13130 series, i.e. migration to 10 % ethanol solution and 3 % acetic acid solution – in both cases for 24 hours at 40 °C). The content of butadiene in the ABS was between 0.07 and 3.1 mg/kg. The result was that no migration of any of the monomers in any of the samples was identified (the detection limit was 0.01 mg/l).

Survey and investigation of migration of monomers in toy materials (Ministry of Environment and Food of Denmark, 2019)
10 products of ABS (analyzed for content of acrylonitrile, butadiene and styrene)
5 products of PS (analyzed for content of styrene)
2 products of SEBS (analyzed for content of styrene)
2 products of SBC (analyzed for content of butadiene and styrene)

Monomer	Material	Content measured in toys in this project (mg/kg)	Other measurements in toys (mg/kg)	Other measurements in other products (mg/kg)
Vinyl chloride	PVC	< 0.1	< 0.1	< 1 (raw material)
Acrylonitrile	ABS	8 - 64	< 0.01 - 55	0.15 - 50 (FCM)
Butadiene	ABS	0.23 - 1.55	< 0.01 - 5	0.06 - 1.7 (FCM)
	SBC	< 0.1 - 0.2	*No data*	*No data*
	SBS	*Not analysed*	< 0.1	*No data*
Styrene	ABS	595 - 1350	1.3 - 2600	Max. 3042 (FCM)
	PS	230 - 490	Max. 800	345 - 1000
	SBC	< 0.2 - 8	*No data*	*No data*
	SEBS	< 0.2	< 0.05 - 1.1	*No data*
	SBR/SBS	< 0.1	*No data*	*No data*

For ABS 1,3-BD is identified at the lowest levels and is generally below 1 mg/kg but with two products with a content above 1 mg/kg (with a content of 1.05 mg/kg and 1.55 mg/kg). On average, the content of butadiene is 0.57 mg/kg in the 10 examined products. This corresponds to results from the literature

which states levels from 0.06 to 1.7 mg/kg – however, with a single survey of toys with a content of up to 5.3 mg/kg.
Migration analyses were carried out on two products of ABS and two products of PS with the highest levels of acrylonitrile, butadiene and styrene respectively. The result was that no migration from any of the monomers (acrylonitrile, butadiene and styrene) were identified, either to artificial sweat, 20 % ethanol, artificial saliva, demineralised water or stomach acid from either ABS or PS in any of the in total four examined toy materials.

Synthetic Turf Field Recycled Tire Crumb Rubber Research Under the Federal Research Action Plan. Final Report Part 1 – Tire Crumb Rubber Characterization Volume 1 (and Volume 2) (EPA 2019)
VOC measurements at 25 °C : For tire crumb rubber from tire recycling plants, 1,3 butadiene was not detected in any of the 27 samples. For tire rubber infill from synthetic turf, 1,3-butadiene measurements were above quantifiable limits in only 5 of the 38 samples and the emission factors were low for these few samples (≤1.0 ng/g/h).
VOC Emissions at 60 °C : Similar to tests at 25 °C measurements, 1,3-butadiene was above quantifiable limits in4 of 37 samples, and the emission factors were low (≤ 1.3 ng/g/h).

Determination of 1,3-Butadiene Migrated from Butadiene-Based Polymers to Air and Water Using Sorbent Tubes and Purge-and-Trap (Anara Omarova et al, 2021)
The study is centered around the validation of the method. There is not enough information about the sample they took from a SBR shoe and ABS toys to make any inferences (number of samples, content of BD in sample, size of sample, etc.). Extraction in water was done for 24 h at 104 °F (extreme condition), while extraction in air was done at room temperature.
The 1,3-butadiene was not detected in migration air and water from ABS toys but was found in both air and water after incubation with SBR-based sample. The concentrations of 1,3-butadiene migrated from SBR samples were 0.91±0.09 µg m−3 in air and 0.044±0.003 µg L−1 in water.

Comments by Juan Ramon Salinas, Managing Director and Chief Executive Officer, International Institute of Synthetic Rubber Producers Inc. EPA-HQ-OPPT-2018-0451-0027 (IISRP, 2020)
The submitted information comprises a slide deck that provides a mass balance of inputs and outputs of 1,3-BD in both the Emulsion and Solution Processes for producing synthetic rubber products, information on the residual 1,3-BD levels in synthetic rubbers, and information on occupational exposure to 1,3-BD during the manufacture of synthetic rubber. It also includes a substantial number of safety data sheets for various common grades of synthetic rubber products.

Appendix 2:
Studies evaluating migration of VOCs from plastic products/ polymers, but no reference to detection of Butadiene (not clear if not quantified or not measured)

Temperature driven variations in VOC emissions from plastic products and their fate indoors: A chamber experiment and modelling study (Beel, 2023)

Influence of polymer additives on gas-phase emissions from 3D printer filaments (Potter, 2021. EPA study)

Monitoring the BTEX Volatiles during 3D Printing with Acrylonitrile Butadiene Styrene (ABS) Using Electronic Nose and Proton Transfer Reaction Mass Spectrometry (Wojnowski, 2020)

Identification of plastic toys contaminated with volatile organic compounds using QCM gas sensor array (Oleneva, 2020)

Particle and volatile organic compound emissions from a 3D printer filament extruder (Byrley, 2020 EPA study)

Emissions of VOCs From Polymer-Based Consumer Products: From Emission Data of Real Samples to the Assessment of Inhalation Exposure (Even, 2019)

VOC Emissions and Formation Mechanisms from Carbon Nanotube Composites during 3D Printing (Potter, 2019. EPA study)

The emissions of monoaromatic hydrocarbons from small polymeric toys placed in chocolate food products (Marc, 2015)

Environmental-sanitary risk analysis procedure applied to artificial turf sports fields (Ruffino et al, 2013)

Contamination in food from packaging material (Lau and Wong, 2000)

Air Emissions from Carpet Manufacturing Processes (Mulholland, ??)

Modeling emissions of VOCs from new carpets (Little, 1994)