Overview of the 2024 Draft Risk Evaluation for 1,3-Butadiene

Introduction to TSCA and 1,3-Butadiene

OFFICE OF POLLUTION PREVENTION AND TOXICS (OPPT)
U.S. ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA)
APRIL 1, 2025

ACKNOWLEDGEMENTS

Thank you to:

Authors and/or Contributors
Kiet Ly and Aderonke Adegbule, Sarah Au, Melody Bernot, Odani Bowen, Marcy Card, Jone Corrales, Scott Drewes, Marc Edmonds, Victoria Ellenbogen, Pat Fontenot, Ross Geredien, Sheila Healy, Ann Huang, Keith Jacobs, June Kang, S. Xiah Kragie, Grace Kaupas, Yadi Lopez, Azah Abdalla Mohamed, David Popko, Brooke Porter, Abhilash Sasidharan, Kelley Stanfield, Michael Stracka, Cory Strope, Catherine Taylor, Abby Ulmer, Joe Valdez, Leora Vegosen, and Jason Wright.

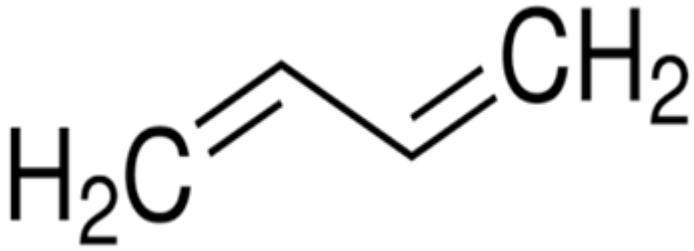
Technical Support: Mark Gibson and Hillary Hollinger

Contract Support: ICF (Contract No. 68HERC23D0007), ERG (Contract No. 68HERD20A0002 and GS-00F-079CA), SRC, Inc. (Contract No. 68HERH19D0022)

Technical Experts: Thomas Bateson and Leonid Kopylev

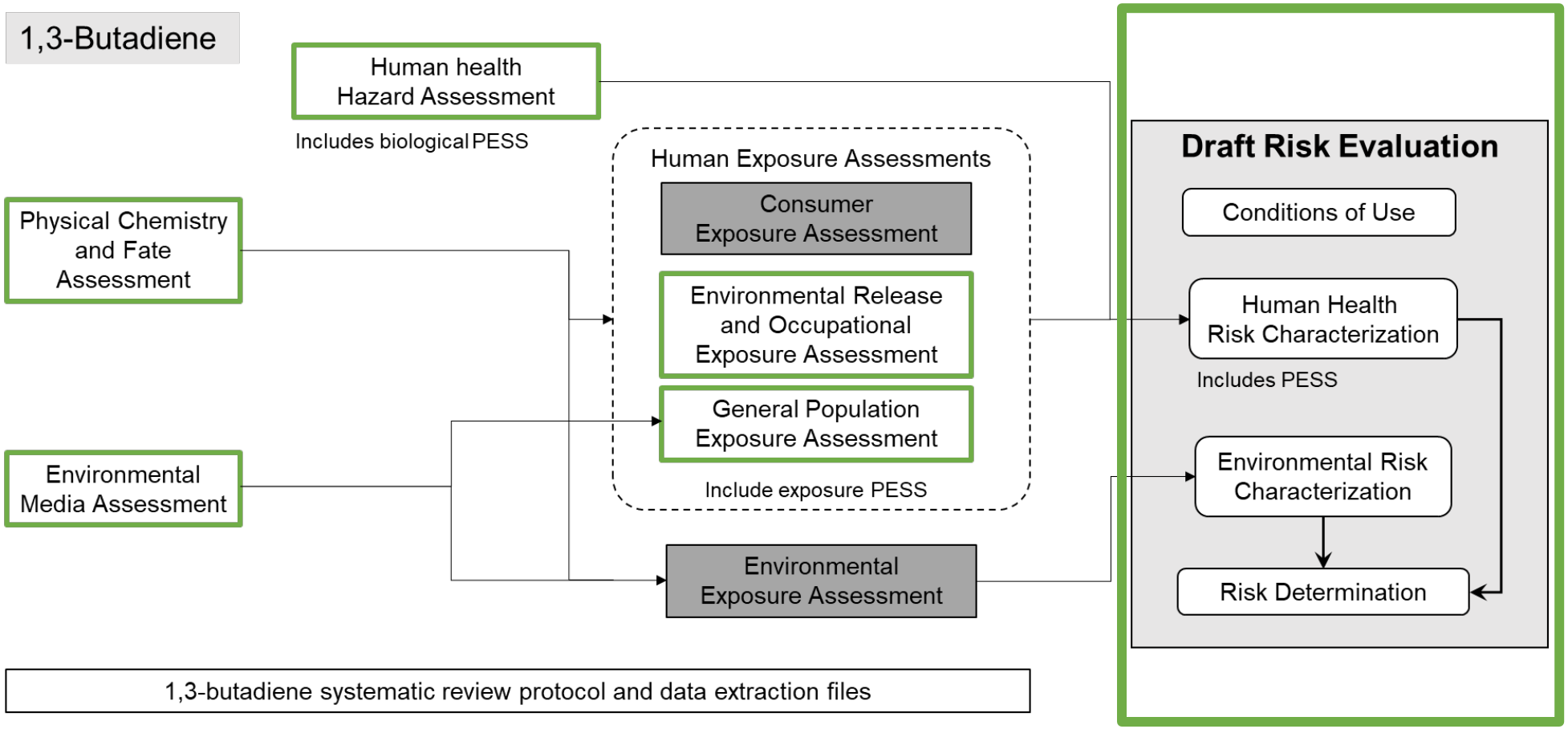
BACKGROUND

- 1,3-Butadiene is a colorless gas produced from petrochemical processing
- TSCA uses for 1,3-butadiene are primarily as a chemical intermediate and as a monomer in the manufacture of rubber, plastics, and resins
- Production volumes between 2016 and 2019 were between 1 billion pounds and 5 billion pounds annually
- Other sources of butadiene exposure come from the combustion of fuel, wood, and tobacco
  - Exposure to 1,3-butadiene as product of combustion will not be quantitatively evaluated



1,3-Butadiene Representative Structure
(CASRN: 106-99-0)

1,3-BUTADIENE DOCUMENT MAP



TSDs outlined in **green**; shaded boxes indicate qualitative narrative in main RE without separate TSD

Figure 2-6 in the *Draft Risk Evaluation for 1,3-Butadiene*

Included as part of current SACC Review

EPA United States Environmental Protection Agency

PRESENTATION OUTLINE

SACC Presentation

1,3-Butadiene in the Environment	Human Health Hazard	General Population Exposure	Occupational Exposure	Organization

Charge Questions

1	5 a-f	2, 3	4	6

PRESENTATION OUTLINE

Presenter	Presentation Section	Charge Question
Sheila Healy	Introduction	NA
Aderonke Adegbule	Environmental Exposure and Analysis of 1,3-Butadiene in the Environment	1
Keith Jacobs	Human Health Hazard Introduction	NA
Abhilash Sasidharan	1,3-Butadiene Non-Cancer Human Health Hazard Assessment	5a, 5b, 5c, 5d
Ann Huang	1,3-Butadiene Cancer Human Health Hazard Assessment	5e, 5f
Kiet Ly	1,3-Butadiene General Population Exposure	2
Kiet Ly	1,3-Butadiene Consumer Exposure Qualitative Assessment	3
Catherine Taylor	1,3-Butadiene Occupational Exposure Assessment	4
Kiet Ly	1,3-Butadiene Risk Evaluation Organization and Transparency	6

1,3-Butadiene Draft Risk Evaluation and Technical Support Documents:
https://www.regulations.gov/docket/**EPA-HQ-OPPT-2024-0425**

EPA United States Environmental Protection Agency

INTRODUCTION TO TSCA

Sheila Healy Ph.D., DABT, OCSPP/OPPT

REGULATORY CONTEXT

TSCA Section 6(b) requires EPA to conduct risk evaluations to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to potentially exposed or susceptible subpopulation(s) (PESS) identified by EPA as relevant to the risk evaluation under the conditions of use (COU)

EPA United States Environmental Protection Agency

U.S. EPA REQUIREMENTS UNDER TSCA

- Evaluate existing chemicals with clear and enforceable deadlines
- Must use **best available science** using **reasonably available information** and make decisions based on the **weight of scientific evidence**
- Develop a risk-based chemical assessment without consideration of costs or other non-risk factors
- Consider risks to potentially exposed or susceptible subpopulations (PESS) determined to be relevant to the evaluation

TSCA RISK EVALUATIONS OVERVIEW

- The risk evaluation considers exposure and hazard to determine whether a chemical substance presents an unreasonable risk to human health or the environment under the conditions of use.
- The risk evaluation is the **primary science support document** the Agency uses if it is necessary to issue regulations to address unreasonable risks identified as part of the evaluation.
- To the extent the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science… **[Section 26(h)]**

KEY SCIENCE TERMS FROM TSCA

EPA will document that the risk evaluation is consistent with the **best available science** and based on the **weight of scientific evidence**. In determining best available science, EPA shall consider as applicable:

(i) The extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information;

(ii) The extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture;

(iii) The degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented;

(iv) The extent to which the variability and uncertainty in the information—or in the procedures, measures, methods, protocols, methodologies, or models—are evaluated and characterized; and

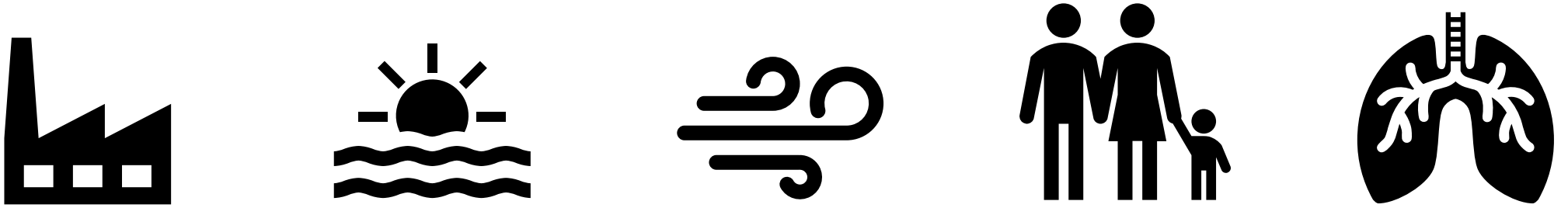
(v) The extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies or models.

EPA United States Environmental Protection Agency

WEIGHT OF SCIENTIFIC EVIDENCE

- To meet the law's requirement to base decisions in TSCA risk evaluations on the **weight of scientific evidence (WOSE)**, EPA relies on established Agency guidance documents which provide consistency and formality to a process that looks to integrate multiple lines of evidence.
- The WOSE assessment is based on the strengths, limitations, and interpretation of data available, information across multiples lines of evidence and how these different lines of evidence may or may not fit together when drawing conclusions.
- The WOSE assessment examines multiple lines of evidence from scientifically relevant published or publicly available studies in the peer reviewed scientific journals, studies conducted in accordance with OECD or EPA guidelines, and any other studies, scientific information, or lines of evidence that are of sufficient quality, relevance, and reliability, are evaluated across studies and endpoints into an overall assessment.
- EPA has provided a summary WOSE narrative or characterization to accompany a detailed analysis to transparently describe the conclusion(s), as well as explain the selection of the studies or effects used as the main lines of evidence and relevant basis for conclusions.

TSCA RISK ASSESSMENT CONSIDERATIONS



Source	Pathway	Media	Populations	Routes
• **Industrial Releases to Air**, Land and Water • Articles and Products	• **Ambient Air** • Land • Water • Indoor Air	• **Air** • Biosolids • Groundwater • Sediment • Soil • Surface Water	• **General Population** • **Workers** • Environmental Organisms • Consumers	• **Inhalation** • Dermal • Oral

SCIENCE QUALITY AND TRANSPARENCY

Internal

- Peer Review
  - Technical Teams
  - Senior Scientists
  - Management
- Collaboration
  - Office of Research and Development (ORD)
  - Office of Air and Radiation (OAR)

External

- Public Comment
- Peer Review
  - Science Advisory Committee on Chemicals (SACC)
- Stakeholder Engagements

EPA United States Environmental Protection Agency

Thank you for your attention

EPA United States Environmental Protection Agency

ENVIRONMENTAL EXPOSURE ASSESSMENT AND ANALYSIS

Addie Adegbule, Ph.D., OCSPP/OPPT

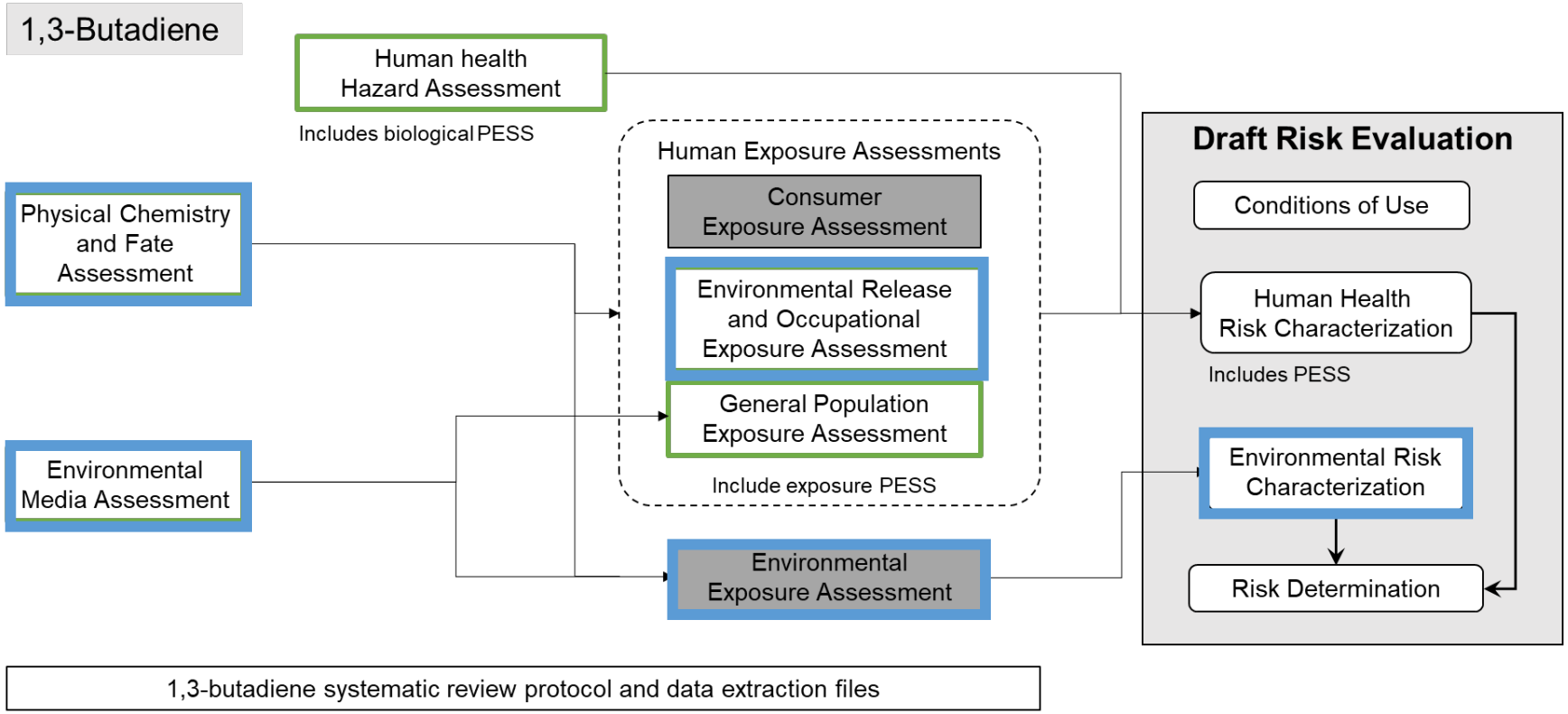
Melody Bernot, Ph.D., OCSPP/OPPT

Charge Q1

Environmental Exposure Assessment and Analysis

- *Draft 1,3-Butadiene Risk Assessment:*
  - ***Section 3***: Chemistry and Fate and Transport of 1,3-Butadiene
  - ***Section 4***: Releases and Concentrations of 1,3-Butadiene in the Environment
  - ***Section 5***: Environmental Risk Assessment
- *Support Document*: Draft Chemistry, Fate, and Transport Assessment
- *Support Document:* Draft EPI Suite Modeling Results
- *Support Document*: Draft Environmental Media Concentrations
- *Support Document:* Draft WQP Monitoring Data 2011 to 2023
- *Support Document*: Draft Environmental Release and Occupational Exposure Assessment

Charge Questions	Reference Documents
Charge Question 1 (Environmental Exposure Assessment and Analysis)	Draft Chemistry, Fate and Transport Assessment for 1,3-Butadiene https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0013 Draft Environmental Media Concentrations for 1,3-Butadiene https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0014



TSDs outlined in **green**; shaded boxes indicate qualitative narrative in main RE without separate TSD

Figure 2-6 in Draft 1,3-Butadiene Risk Evaluation

Charge Q1

Technical Support Document (TSD) and Sections of Risk Evaluation Related to this Charge

Draft Assessment of 1,3-Butadiene Exposure in the Environment

Outline

1. Overview of Chemistry, Fate, and Transport Assessment
2. Overview of Environmental Releases
3. Overview of Monitoring Data
4. Key Conclusions for the Land Pathway
5. Key Conclusions for the Water Pathway

Charge Q1

1,3-BUTADIENE CHEMISTRY, FATE AND TRANSPORT

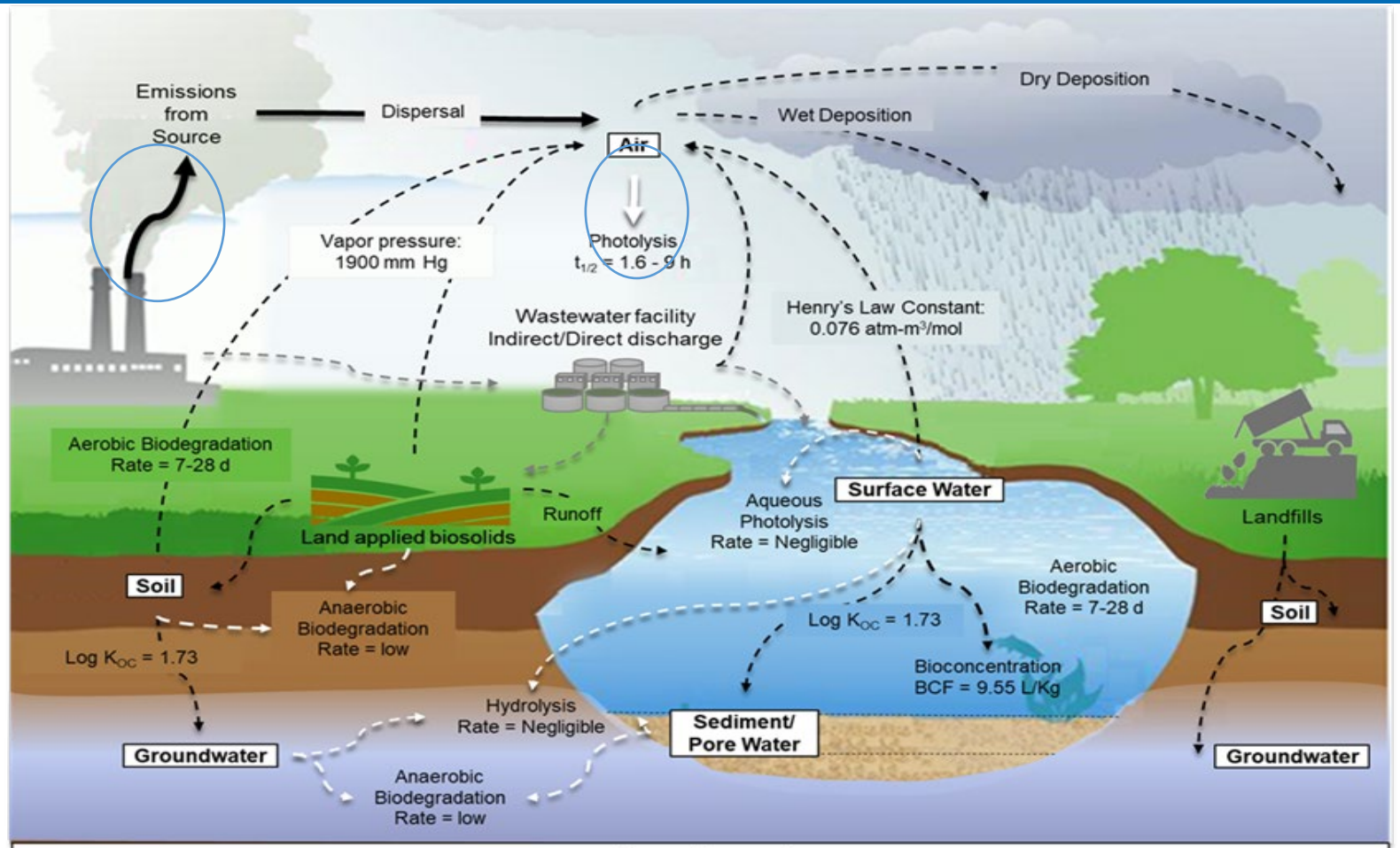


Figure 4-1 from Draft Physical Chemistry, Fate and Transport Assessment for 1,3-Butadiene

Charge Q1

1,3-BUTADIENE CHEMISTRY, FATE AND TRANSPORT

- Highly volatile gas (HLC = 0.076 atm m^3/mol; VP = 1900 mm Hg)
- Not very soluble in water (735 mg/L at 20 °C)
- Highly reactive ($t_{1/2}$=1.6 to 9 hours) and photodegrades to yield formaldehyde and acrolein
- Low sorption potential to organic matter in soil, sediments or air particulates (Log K_{oc} = 1.73, Log K_{oa} = 1.50-1.53, Log K_{ow} = 1.99)
- BCF suggests low potential for bioconcentration/bioaccumulation (9.55 L/kg)

Chemistry and fate properties of 1,3-butadiene suggest that it will not persist in water or land

Charge Q1

1,3-BUTADIENE ENVIRONMENTAL RELEASES

- Based on 2021 reported TRI (Toxics Release Inventory) emissions, 99.8% of environmental releases were to air while ~0.1 % of environmental releases were to water and soil
- Fugacity modeling indicates that, once released to air, 1,3-butadiene will mostly remain in air
  - *Assuming half-life values of 2.6 h in air, 28 d in water and soil, 16 wks in sediment*

Based on documented releases to the environment and fugacity modeling, air is expected to be the major pathway of exposure for 1,3-butadiene

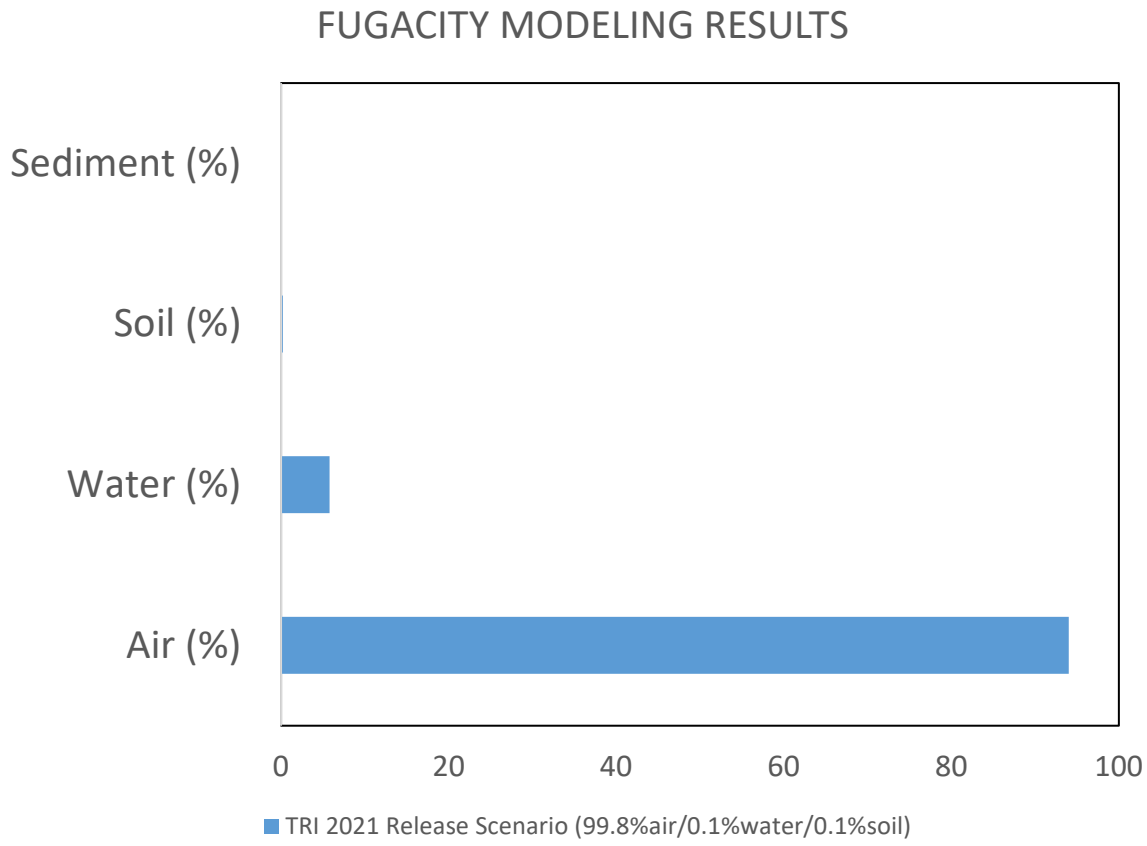


Figure created from Table 3-2 of the Draft Physical Chemistry, Fate and Transport Assessment for 1,3-Butadiene

Charge Q1

1,3-BUTADIENE MONITORING DATA

- Based on data from the Water Quality Portal (WQP), 1,3-butadiene was not detected in 231 surface water samples above method detection limit (MDL) (0.08 ug/l) from 2012 to 2020 (100% non-detects)
- Based on data from the WQP, 1,3-butadiene is not detected in groundwater samples from 2016 to 2023 (100% non-detects)
    - One sample reported in error (National water information system, NWIS)
    - Few reported samples in Arizona (2 to 40 ug/l) reported in between 2013 and 2014, by STORET, not since, and no MDL reported
- Based on monitoring data from the Third Unregulated Contaminant Monitoring Rule (UCMR3), 1,3-butadiene was detected in only 2 of 36,848 drinking water samples from 2013 to 2015 (99.99% non-detects)

1,3-Butadiene was not detected in the majority of monitoring data (≥99%) for surface water, groundwater and drinking water

KEY CONCLUSIONS FOR THE LAND PATHWAY

- 1,3-Butadiene will not persist on land because
  - 1,3-Butadiene quickly volatilizes from wet or dry soil surfaces (HLC = 0.076 atm m^3/mol; VP = 1900 mm Hg)
  - 1,3-Butadiene does not sorb to organic matter and is not expected to undergo dry deposition
  - Release to land is limited (0.1%)
- Majority (99%) of monitoring data indicate 1,3-butadiene is not detected in groundwater
- 1,3-Butadiene has a low potential to bioaccumulate (BCF of 9.55 L/kg)

These conclusions support EPA's decision to develop a qualitative assessment of 1,3-butadiene contributions to land (groundwater, soil) exposure for both human and environmental risk

EPA United States Environmental Protection Agency

KEY CONCLUSIONS FOR THE WATER PATHWAY

- 1,3-Butadiene will not persist in water
  - 1,3-Butadiene quickly volatilizes from water (HLC = 0.076 atm m^3/mol)
  - 1,3-Butadiene does not significantly sorb to organic matter in sediments (log K_{OC} = 1.73, Log K_{OW} = 1.99)
  - Environmental releases to water are a small component of releases (~0.1%)
- Monitoring data indicates that 1,3-butadiene is not detected in surface water (WQP NWQMC 2022)
- 1,3-Butadiene was not detected in the majority (>99.99%) of drinking water monitoring data (UCMR 3)
- 1,3-Butadiene does not bioaccumulate (BCF of 9.55 L/kg)

These conclusions support EPA's decision to develop a qualitative assessment of 1,3-butadiene contributions to water (surface water, sediments, drinking water) exposure for both human and environmental risk

EPA United States Environmental Protection Agency

Thank you for your attention

EPA United States Environmental Protection Agency

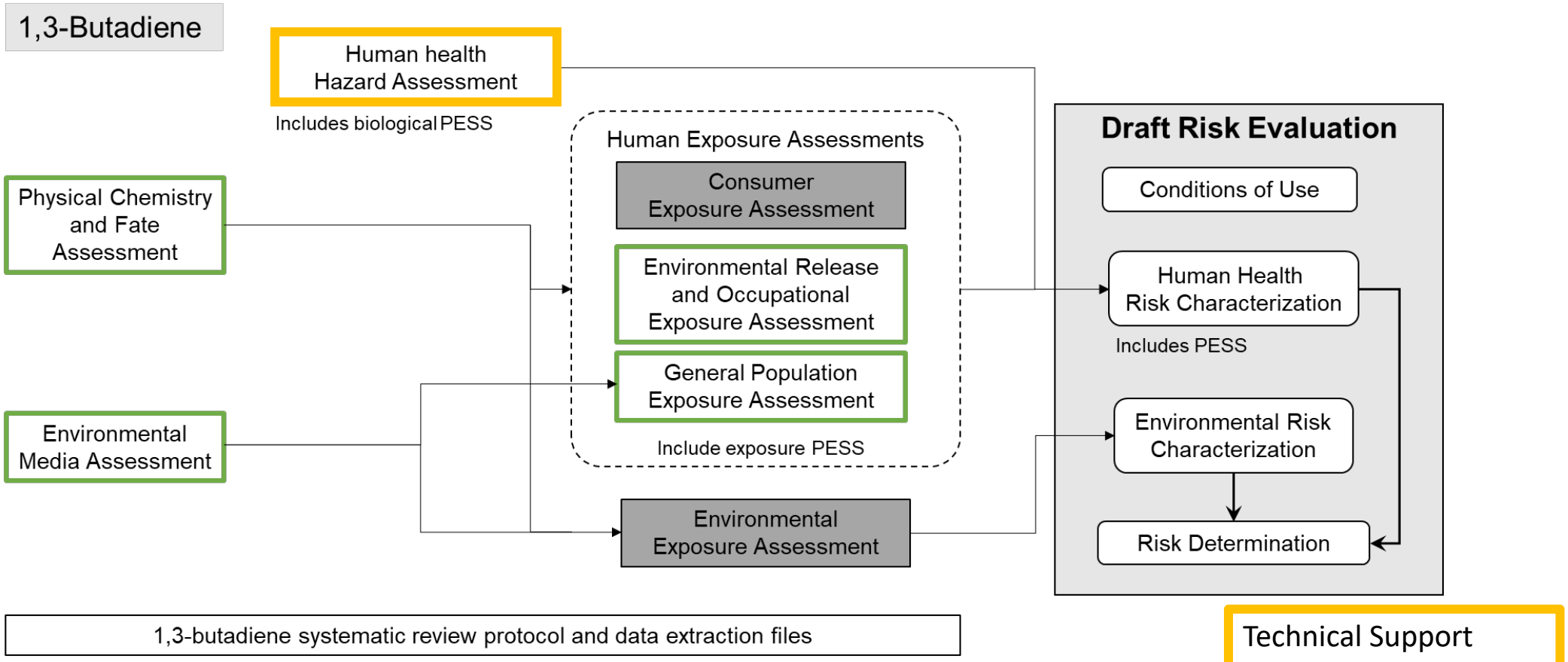
1,3-BUTADIENE HUMAN HEALTH HAZARD ASSESSMENT

Keith Jacobs, Ph.D., OCSPP/OPPT

Abhilash Sasidharan, Ph.D., OCSPP/OPPT

Ann Huang, Ph.D., OCSPP/OPPT

Charge Questions	Reference Documents
Charge Question 5a-f (Human Health Hazard Assessment)	Draft Human Health Hazard Assessment for 1,3-Butadiene https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0046



TSDs outlined in **green**; shaded boxes indicate qualitative narrative in main RE without separate TSD

Figure 2-6 in Draft 1,3-Butadiene Risk Evaluation

Technical Support Document (TSD) and Sections of Risk Evaluation Related to this Charge

HUMAN HEALTH HAZARD ASSESSMENT OVERVIEW

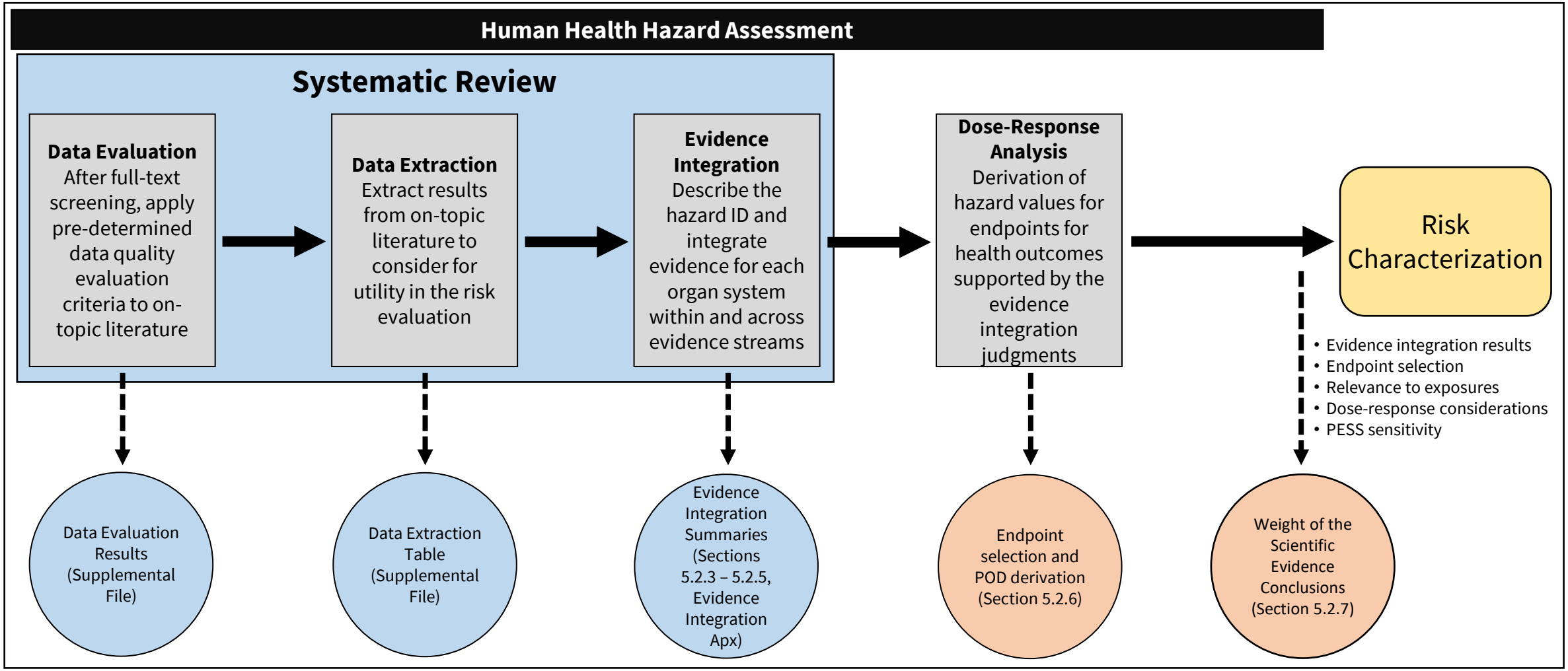


Figure 2-1 in Draft Human Health Hazard Assessment

1,3-BUTADIENE ASSESSMENT HISTORY

- **EPA Assessment History**
  - ORD IRIS Health Assessment in 2002 – acute/chronic non-cancer and cancer hazard values
- **Other Federal Agencies and States:**
  - ATSDR (2012) – non-cancer hazard reviewed but no hazard values derived
  - Texas TCEQ (2012) – acute/chronic non-cancer hazard values
  - California OEHHA (2013) – acute/chronic non-cancer hazard values
    - Cancer derived separately in 2009 through the Air Toxics Hot Spot Program
- **International**
  - Health Canada (2000) – cancer cohort analysis utilized by EPA IRIS (2002)
  - European Union (2002)
  - WHO (2001)
  - Netherlands RIVM (2009)
  - IARC (2012)
  - Australia NICNAS (2013)

TARGETED FILTERING OF SYSTEMATIC REVIEW REFERENCES

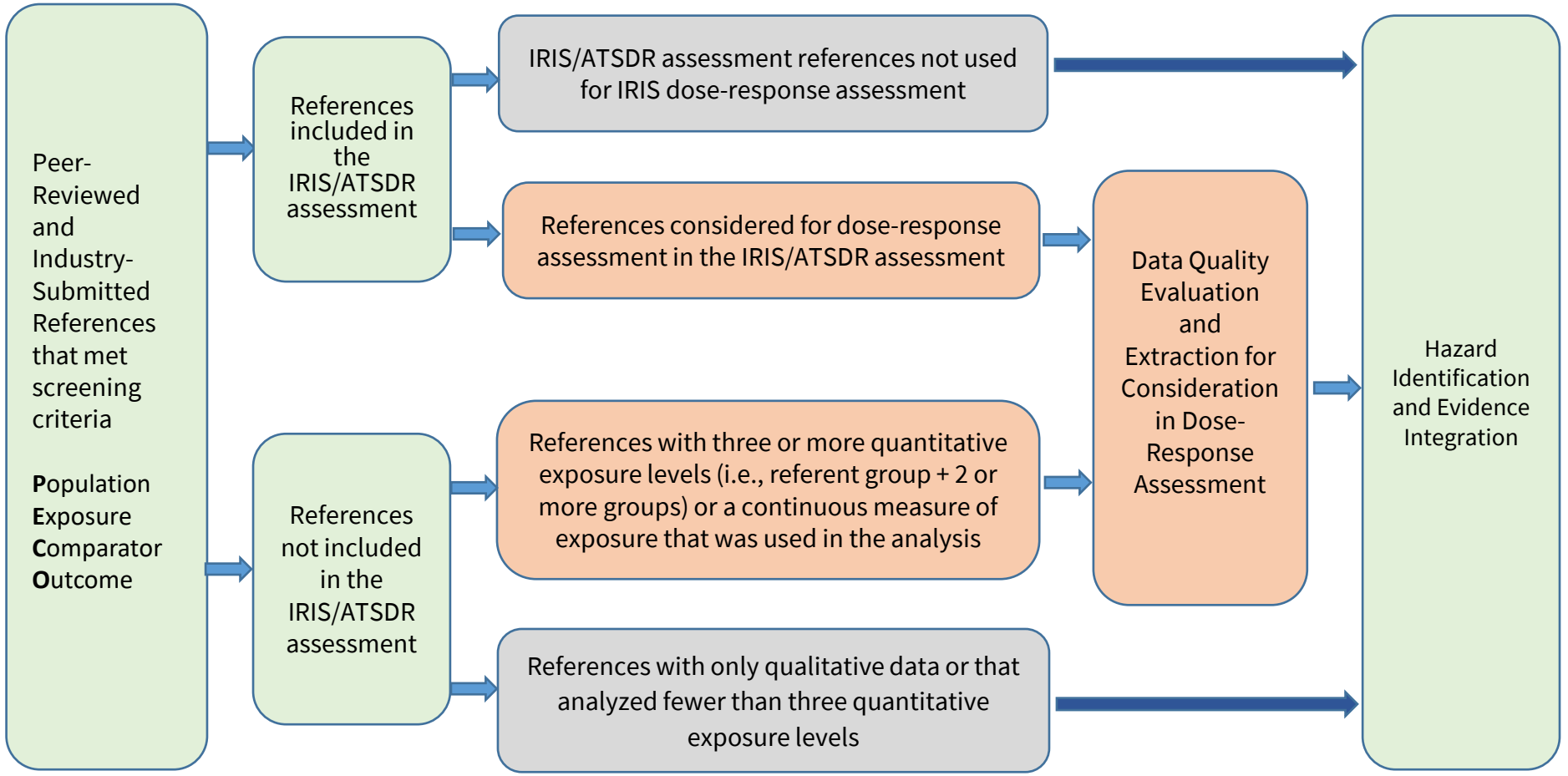


Figure adapted from Figure 4-6 in *Draft Systematic Review Protocol for 1,3-Butadiene*

- In addition to the above process for identifying studies for dose-response, EPA performed a supplemental review of toxicokinetic studies along with information on mode of action and species sensitivity differences published through 2022

EPA United States Environmental Protection Agency

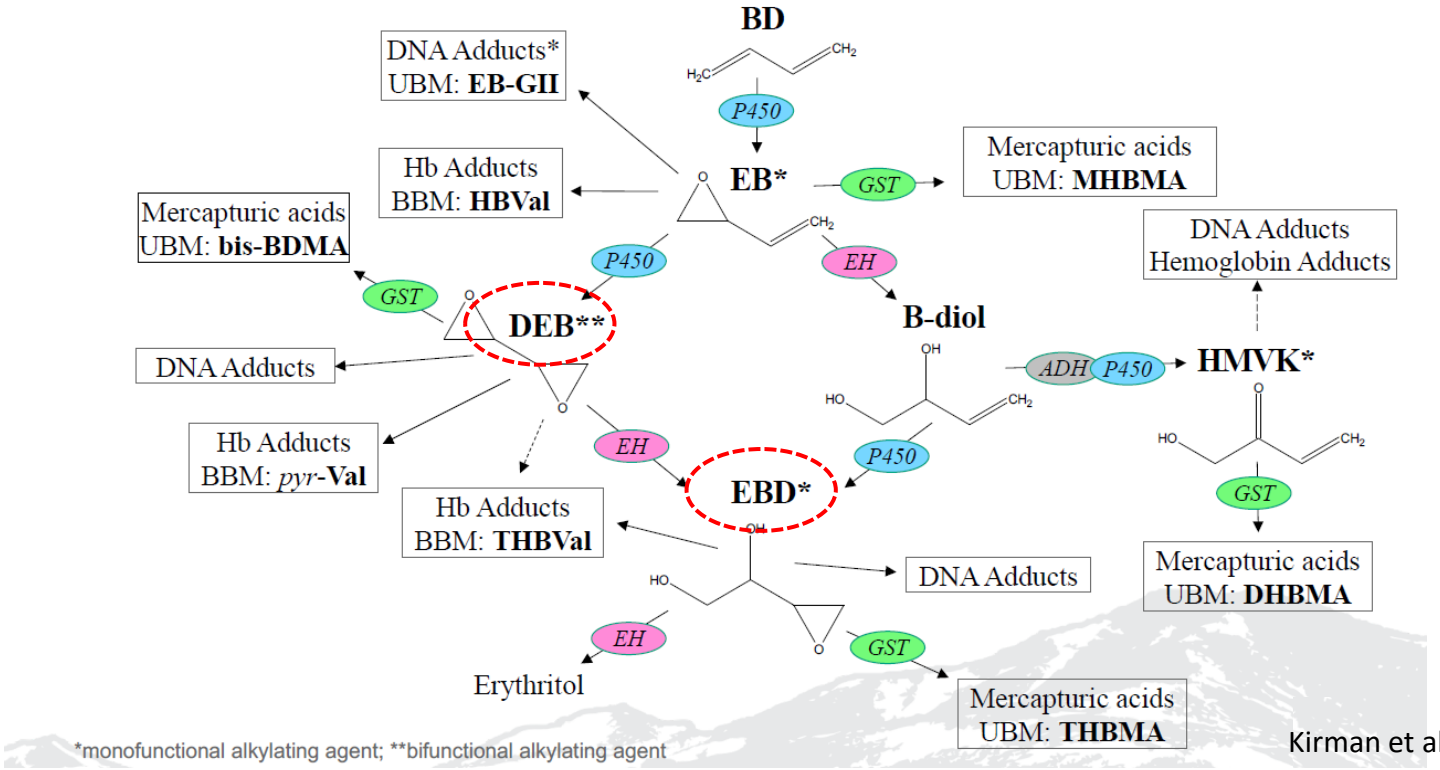
Thank you for your attention

EPA United States Environmental Protection Agency

1,3-BUTADIENE HUMAN HEALTH NON-CANCER HAZARD ASSESSMENT

Abhilash Sasidharan, Ph.D., DABT, ERT, OCSPP/OPPT

METABOLISM OF 1,3 BUTADIENE



Kirman et al. 2022

- **Species variability in BD metabolism:** Mice exhibit a higher efficiency in producing diepoxybutane (DEB), while humans predominantly form epoxybutanediol (EBD)
- **Species-dependent susceptibility:** Mice develop ovarian atrophy and hematologic malignancies at low exposures (6.25ppm), whereas rats exhibit limited toxicity up to 1000ppm, and humans predominantly develop hematopoietic cancers, highlighting distinct interspecies sensitivity

Charge Q5b(i)

1,3-BUTADIENE NON-CANCER HUMAN HEALTH HAZARDS

- **Comprehensive Inhalation Study Database**
  - Primarily subchronic and chronic studies in rodents (rats and mice)
  - Key endpoints: Developmental, reproductive, and hematological effects
- **Existing Assessment Conclusions**
  - EPA IRIS (2002), TCEQ (2010) and OEHHA (2013): Identified ovarian atrophy and fetal weight reduction as the critical endpoints
  - ATSDR (2012): No Minimal Risk Levels (MRLs) based on ovarian toxicity derived due to interspecies metabolic differences and insufficient chemical-specific data
- **Evaluation of Human Relevance of Ovarian Atrophy**
  - The relevance of ovarian atrophy observed in mice to human is uncertain
  - EPA re-evaluated the mode of action (MOA) for ovarian atrophy initially proposed by Kirman et al. (2012), by integrating all available evidence

Charge Q5a,b,c

PROPOSED MODE OF ACTION (MOA) ANALYSIS FOR OVARIAN ATROPHY

KE 1: Bioactivation

- Relative DEB levels follow the pattern: mice >> rats > humans
- Oxidative metabolism is much more active in mice
- EB causes ovotoxicity only in mice (not rats); DEB affects both species, but mice are more sensitive
- VCH (an analog) is more active in mice vs. rats, especially in its diepoxide form

KE 2: Distribution of metabolites

- DEB has been detected in the ovary of both rats and mice, at higher concentrations in mice
- EB also has been detected in rat ovary

KE 3: Follicle destruction

- VCH causes ovotoxicity via follicle depletion, and the diepoxide form (VCD) activates apoptotic signaling in follicles
- DEB activates mitochondrial apoptosis in lymphoblasts.

KE 4: Ovarian failure

- Follicle loss reduces estrogen levels, leading to ovarian dysfunction
- DNA damage, oxidative stress, and inflammation may be major contributors

Figure 4-1 in Draft 1,3-Butadiene Risk Evaluation

Charge Q5b(ii)

OVARIAN ATROPHY IN MICE: RELEVANCE TO HUMAN HEALTH

- EPA followed the IPCS Mode of Action and Human Relevance Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans (Boobis et al., 2008) - four questions were addressed.
- EPA concluded that there *is* sufficient evidence to establish an MOA (Q1).
- Human relevance *cannot be excluded* based on qualitative (Q2) or quantitative differences (Q3).
- There *are* key quantitative differences in key events (Q4) that must be considered in applying mice data to humans.

Charge Q5b(iii)

DATA DERIVED EXTRAPOLATION FACTORS (DDEF)

- Dosimetric modifications to hazard values for ovarian toxicity (as suggested by Q4 in Boobis et al., 2008) could potentially be applied through derivation of data derived extrapolation factors (DDEFs) in accordance with EPA guidance (EPA, 2014).
  - Kirman et al., 2012; 2022 attempted to derive a DDEF for ovarian toxicity based on surrogate measurements of blood metabolite concentrations and relative cytotoxicity
- DDEF applications require a strong quantitative understanding of the MOA, as well as the target tissue and the relevant type of exposure response (EPA, 2014).
  - There is uncertainty in quantifying metabolite levels in humans and at varying exposures
  - The potential influence of EBD (the primary metabolite in humans) on the MOA is unknown
- Therefore, derivation of a DDEF is not supported.
- *Instead, EPA has preliminarily concluded that ovarian atrophy observed in mice is not appropriate for quantitative use in human health risk assessment*

NON-CANCER HAZARD OUTCOMES

Maternal/ Developmental Toxicity	• Epi: Slight evidence of increased risk of autism • Animals: Body weight reduction, skeletal variations and malformations • Potentially due to epoxide metabolites but no evidence for specific species
Male Reproductive Toxicity	• No human data available • Animals: Dominant lethality and reduced testis weight and sperm count • Genotoxic effects to sperm are associated with male infertility
Hematological Effects	• Human data inconclusive, ↓Hb • Animals: Dose- and duration-response changes indicative of anemia • Animals: Mild spleen effects • Genotoxicity in bone marrow may contribute to hematological effects

Due to insufficient information on the mode of action and the role of specific metabolites, EPA applied default dosimetric adjustments instead of deriving data-derived extrapolation factors

Charge Q5c(i)

NON-CANCER ENDPOINTS FOR ACUTE EXPOSURES

- EPA determined that acute exposure to 1,3-butadiene at levels relevant to humans are unlikely to cause significant adverse health effects.
- Acute effects in humans or animals occurred only at very high concentrations (thousands of ppm), which far exceed typical exposure levels. These effects are generally mild and transient (e.g., eye irritation or difficulty focusing).
- Animal studies indicating more severe effects (e.g., developmental or reproductive toxicity) require repeated exposure rather than a single acute event.

BENCHMARK DOSE MODELING AND POINTS OF DEPARTURE

Benchmark dose (BMD) modeling was conducted to refine points of departure (PODs) for maternal, developmental, and hematological toxicity endpoints.

- **Reduced Fetal Body Weight (Intermediate/Chronic)**
  - BMD modeling identified 2.5 ppm ($BMDL_5$ of a dichotomized distribution) as the most sensitive POD, based on developmental effects observed in mice.
- **Maternal Weight Gain, Supernumerary Ribs, and Dominant Lethality (Intermediate/Chronic)**
  - $BMDL_{1SD}$ of 10.4 ppm was determined for reduced maternal weight gain during gestation in mice, and $BMDL_{1SD}$ of 48.9 ppm in rats.
  - $BMDL_5$ of 2.9 ppm and $BMDL_{10}$ of 6.1 ppm were modeled for supernumerary ribs, though the endpoint's relevance to humans remains uncertain.
  - A $BMDL_5$ of 4.83 ppm was modeled for dominant lethality in mice, with some uncertainties about the most appropriate BMR.
- **Anemia (Chronic)**
  - Anemia endpoints (lowest $BMDL_{1SD}$ = 3.91 ppm) were modeled for three blood measures.

Charge Q5c(ii-iii)

POD SELECTION FOR RISK ESTIMATION

Weight of Scientific Evidence

- Fetal body weight in mice ($BMDL_5$ = 2.5 ppm) was identified as the most reliable, sensitive endpoint for intermediate and chronic scenarios.
- Robust overall confidence; associated with multiple related outcomes observed across species and within a few fold of other co-critical effects.
- Fetal weight reduction was consistently observed in rats at higher concentration (Hazleton Labs, 1981a; WIL Research, 2003).

A total uncertainty factor (UF) of 30 proposed as the benchmark MOE

- Intraspecies UF (UF_H): 10x (human variability)
- Interspecies UF (UF_A): Reduced from 10x to 3x (animal-to-human)

Proposed Non-Cancer Hazard Value for 1,3-butadiene

Target Organ System	Species	Duration	Study POD/Type	Effect	HEC (ppm) [mg/m³]	Uncertainty Factors (UFs)	Reference	Overall Quality Determination
Intermediate/chronic exposure scenarios								
Maternal/ Developmental	**Mouse (Male)**	**10 days throughout gestation (GD 5–16)**	**LOAEL = 40 ppm**	**Reduced fetal body weight and other associated endpoints**	**$BMDL_5$ = 2.5 ppm (5.5 mg/m³)**	**UF_A= 3; UF_H=10; Total UF=30**	**(Battelle PNL, 1987b)**	**Medium**

Adapted from Table 8-1 in the *Draft Human Health Hazard Assessment for 1,3-Butadiene*

Charge Q5c (i)

BMD MODELING RESULTS FOR THE PROPOSED POD

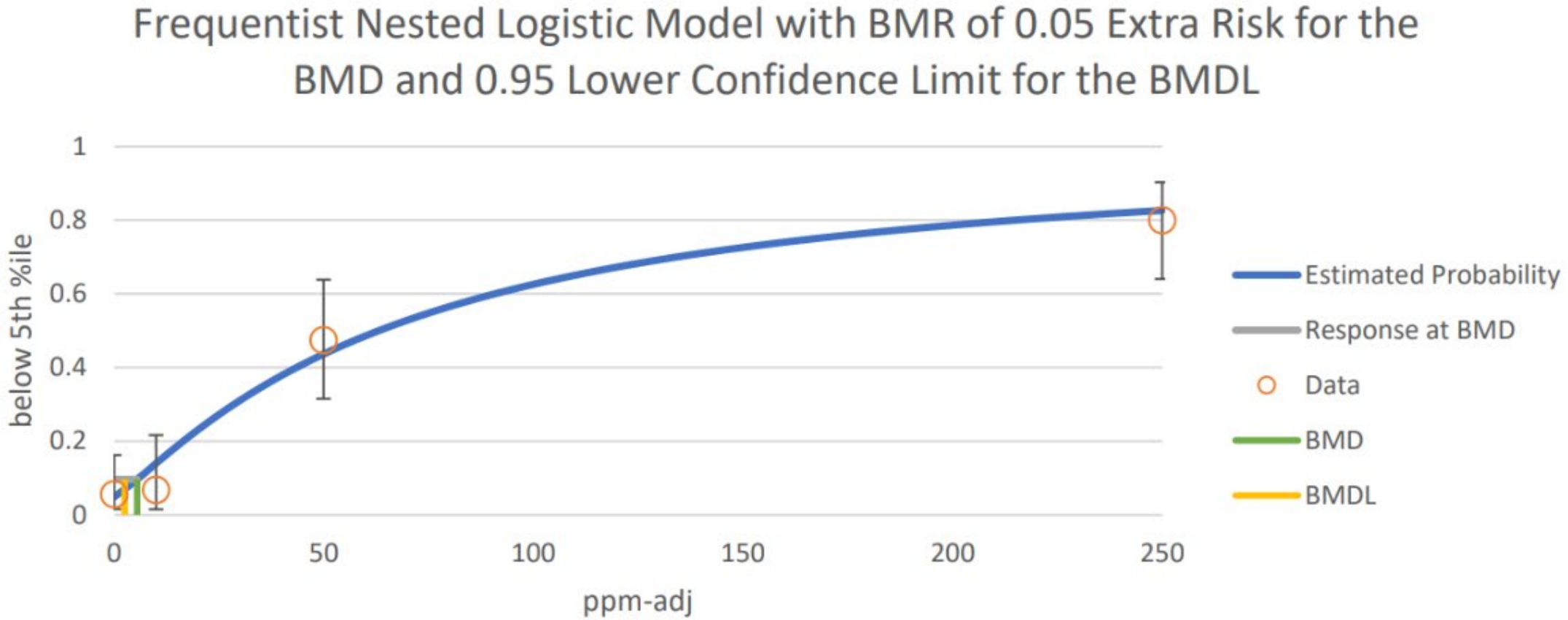


Figure 1-16 in *Draft Benchmark Dose Modeling Results for 1,3-Butadiene*

- These results demonstrated adequate model fit according to software cutoffs and good visual model fit with low BMD:BMDL spread (~2x) and within close range of the lowest dose tested.

Charge Q5c(iv)

UNCLEAR FETAL WEIGHT REDUCTION MOA AND CHALLENGES IN APPLYING DDEF

- Kirman et al. (2022) proposed a DDEF based on either a cytotoxicity or "general toxicity" MOA, linking fetal weight effects to maternal toxicity.
  - Both proposed MOAs lack experimentally validated key events directly linking 1,3-butadiene exposure to fetal weight reduction due to several uncertainties and data gaps:
    - Limited information on metabolism during pregnancy and in fetal tissue with uncertainty regarding the role of primary metabolite(s) (DEB, EB, or EBD) in driving the toxicity.
    - Data are derived from diverse cell lines (e.g., human bone marrow, TK6 cells, rodent fibroblasts, chicken lymphoid cells) with wide variability (Kirman, 2022)and no evidence linking these responses to fetal weight reduction in mice.
    - MOAs from one tissue or outcome cannot be extrapolated to support a DDEF for another (EPA, 2014).
  - Fetal weight reductions occur at lower doses than maternal weight and other reproductive outcomes, suggesting that fetal weight may be more sensitive or mechanistically distinctive.
- Due to the poorly defined MOA and the identified uncertainties, the application of DDEF is deemed inappropriate in accordance with EPA guidance (U.S. EPA, 2014).

Charge Q5c

CONCLUSION AND KEY POINTS

- EPA concluded that ovarian atrophy in mice is not suitable for quantitative use in human risk assessment because mice exhibit substantially greater susceptibility to 1,3-butadiene, and cross-species differences cannot be quantified confidently.
- Reduced fetal weight, identified in a developmental mouse study, was the most sensitive and robust endpoint for risk characterization of intermediate and chronic exposures.
- The available evidence does not support derivation of a POD for acute exposures, given the limited data and uncertainties.
- There is robust overall confidence in the non-cancer POD for intermediate and chronic scenarios.

For more information, see the Draft Human Health Hazard Assessment for 1,3-butadiene

Charge Q5a,b,c

EPA United States Environmental Protection Agency

Thank you for your attention

EPA United States Environmental Protection Agency

1,3-BUTADIENE CANCER HAZARD ASSESSMENT

Ann Huang, Ph.D., OCSPP/OPPT

Abhilash Sasidharan, Ph.D., DABT, ERT, OCSPP/OPPT

Outline for Cancer Hazard Assessment

- Evidence integration
- Weight of the evidence
- Cancer dose-response assessment
- IUR derivation for leukemia and bladder cancer

CANCER HAZARD IDENTIFICATION

- History
  - EPA IRIS (2002) published IUR for leukemia: 0.08 per ppm, based on an occupational epidemiological study (US-Canadian styrene-butadiene rubber (SBR) cohort study) with male workers
  - ATSDR (2012): epidemiological data concluded that occupational exposure to 1,3-butadiene was associated with increased mortality
  - IARC (2012): recognized sufficient evidence of carcinogenicity only for cancers of the hematolymphatic system
  - NTP (2021): butadiene is a known human carcinogen for leukemia
  - Since IRIS (2002), US-Canadian styrene-butadiene rubber cohort study had multiple updates: additional follow-up years, inclusion of female workers, and refined exposure assessment
- EPA OPPT cancer assessment focuses on:
  - Studies published after EPA IRIS (2002)
  - Inhalation unit risk (IUR) for leukemia based on updated cohort data

Charge Q5e((i),f(i)

Cancer Evidence Summary

- Epidemiological studies (73 studies):
  - Robust evidence showed 1,3-butadiene is a carcinogen for leukemia
  - Moderate evidence showed 1,3-butadiene is positively associated with bladder cancer
  - Other cancer sites: Slight or no evidence
- Animal toxicology (35 studies):
  - 1,3-butadiene is a multisite carcinogen, as evidenced in both rodent species, with a higher carcinogenic susceptibility observed in mice (6.25 ppm) compared to rats (1000 ppm)
  - Lymphohematopoietic cancers were only observed in mice
- Mechanistic evidence:
  - Metabolic activation of 1,3-butadiene produces DNA reactive metabolites (EB, EBD, DEB) that form DNA adducts, inducing mutations in critical genes and chromosome aberrations, ultimately driving tumor formation
- Cancer classification based on EPA Cancer Guidelines: 1,3-butadiene is considered "carcinogenic to humans"

Charge Q5e((i),f(i)

PROPOSED MUTAGENIC MODE OF ACTION (MMOA)

- Epidemiological studies have linked occupational exposure to 1,3-butadiene with increased mortality from various lymphohematopoietic cancers, including leukemia and lymphoma.
- 1,3-Butadiene is a multi-organ carcinogen in laboratory animals, notably inducing lymphomas in mice.
- The development of these cancers is hypothesized to result from the mutagenic potential of one or more 1,3-butadiene metabolites.
- EPA postulates a Mutagenic Mode of Action (MMOA) for lymphohematopoietic cancers caused by 1,3-butadiene.
- This analysis was conducted in accordance with the EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) and the draft Framework for Determining a Mutagenic Mode of Action for Carcinogenicity (U.S. EPA, 2007).

KEY EVENTS SUPPORTING MMOA

The MMOA is supported by evidence categorized into four key events.

KE 1: Bioactivation

- Metabolic activation occurs primarily in the liver via cytochrome P450 enzymes.
- Produces electrophilic intermediates (EB, EBD, and DEB).

→

KE 2: DNA Damage

- Electrophilic metabolites form DNA adducts detectable *in vitro, in vivo*, and in occupationally exposed workers.
- DNA adducts induce mispairing during replication, leading to point mutations, deletions, and chromosomal damage.

→

KE 3: Mutations

- Induces chromosomal aberrations and mutations in critical genes (e.g., K-ras and TP53).
- The mutagenic potential of 1,3-butadiene is supported by numerous positive results from both *in vivo* and *in vitro* mutation assays.

→

KE 4: Cancer Development

- Chronic exposure causes tumors in rodent hematopoietic systems.
- Multiple cohorts link occupational 1,3-butadiene exposure to elevated leukemias, including CML with t(9;22), support a mutagenic mechanism.

See Section 5.3 of *Draft Human Health Hazard Assessment for 1,3-Butadiene* for further details

WEIGHT OF EVIDENCE SUPPORTING MMOA

Key Event	Study Type	Key Findings (Positive vs. Negative)
KE 1: Bioactivation	*In Vitro & In Vivo* (≥10+ studies) Human (≥3+ occupational studies)	Epoxide metabolites detected in ≥10+ animal studies; higher levels in mice. Hemoglobin adducts confirm formation of EB, EBD, DEB in exposed workers.
KE 2: DNA Damage	*In Vitro & In Vivo* (≥15+ studies) Human (≥6+ occupational studies)	≥13+ report DNA adducts (EB, DEB, EBD) and strand breaks; 2 are inconclusive or negative. 5 detect significant DNA damage (adducts); 1 shows minimal effect.
KE 3: Mutations	*In vivo* (≥20+ rodent studies) Human (≥10-20 studies)	Multiple studies (≥15) show gene mutations (e.g., hprt), chromosomal aberrations, micronuclei; rats generally less responsive than mice. Early studies mixed (e.g., 6/10 positive for hprt or SCE), but more recent data consistently show increased micronuclei in highly exposed workers.
KE 4: Cancer Development	*In vivo*(≥2 rodent studies) Human (≥4+ occupational studies)	Rodents: 2 confirm multi-organ tumor formation. ≥4+ link occupational 1,3-butadiene to elevated risk of lymphohematopoietic cancers.

See Section 5.3 of the *Draft Human health Hazard Assessment for 1,3-Butadiene* for further details

MMOA WEIGHT OF EVIDENCE ANALYSIS

Key Observations:

- Consistency: Epidemiological and animal studies consistently demonstrate mutagenic outcomes.
- Temporality: Genetic damage occurs shortly after exposure (e.g., mutations observed within days in animal models).
- Dose-response relationship: Increased exposure correlates with greater genetic damage and cancer incidence.

Strength of Evidence:

- Supported by multiple lines of evidence, including DNA adduct formation, mutations in key genes, and carcinogenic outcomes.
- Both rodent studies and human epidemiological data align with the hypothesized MMOA.

EPA United States Environmental Protection Agency

MUTAGENIC MOA CONCLUSION

- Available evidence supports a mutagenic MOA for 1,3-butadiene in the development of lymphohematopoietic malignancies in both rodents and humans.
- The primary driver of 1,3-butadiene's mutagenic MOA is the formation of electrophilic metabolites, which causes DNA damage and mutations.
- Based on evidence supporting a mutagenic MOA for 1,3-butadiene, a linear cancer assessment approach with the incorporation of Age-Dependent Adjustment Factors (ADAFs) is used to calculate an inhalation unit risk (IUR) for lymphohematopoietic cancer.

Study Selection Criteria in Cancer Dose-Response Assessment

Cancer Type	Human	Animal	Mechanistic
Lymphohematopoietic	Robust	Robust	Robust
Bladder	Moderate	Indeterminate	Slight

Selection of studies for cancer dose-response assessment

- Study selection consideration:
  - Study quality
  - Dose range and exposure-response
  - Strength of the evidence supporting the associated tumor type
  - Relevance
  - Uncertainties
- Epidemiological study evaluation criteria:
  - Study population
  - Exposure assessment
  - Exposure concentrations
  - Statistical analysis
  - Confounder adjustments
  - Estimates of population risk (e.g., relative risk)

Charge Q5e((i),f(i)

Weight of Evidence in Leukemia Dose-Response Assessment

Selection of studies: focus on robust/moderate human evidence

- Weight of Evidence for Leukemia: **ROBUST**
  - 21 leukemia epidemiological publications provided dose-response results
  - 17 out of 21 publications showed a significant positive association
  - 18 out of 21 publications used data from the US-Canadian styrene-butadiene rubber (SBR) worker cohort study

Charge Q5e((i),f(i)

Cancer Dose-Response Assessment

- Recruitment, Follow-up and Expansion of SBR Cohort (US-Canadian styrene-butadiene rubber cohort study):
  - IRIS (2002) includes the data through 1991 and only included male participants
  - Updated exposure assessment (Macaluso, 2004) provided:
    - more specific exposure scenarios
    - verification of parameters
    - further characterized peak exposure

Historical Changes in the SBR Cohort	Period of Recruitment and Follow-Up	Gender of Participant Recruitment	Number of Workers	Number of Deaths
Original study plan	1944–1991	Male	17,964	4,665
Extended follow-up for male workers	1944–1998	Male	17,924	6,237
Expanded recruitment for female workers	1943–2002	Female	4,861	1,198
Extended follow-up for male and female workers	1943–2009	Male and Female	21,087 (16,579 men and 4,508 women)	9,665 (8,214 men and 1,451 women)

Charge Q5f(i)

Study Selection for Leukemia Dose-Response Assessment

- 16 epidemiological publications provided adequate dose-response information
- 13 publications used data from SBR cohort (US-Canadian styrene-butadiene rubber cohort study) during 2002-2024:
  - Updated exposure assessment (Macaluso, 2004)
  - Population inclusion: both male and female study participants

Study Selection for Leukemia Dose-Response Assessment

- EPA used SBR cohort (US-Canadian styrene-butadiene rubber cohort study) data for dose-response assessment:
  - Study design: a cohort study with 60+ follow-up years
  - Regression coefficients from a dose-response model
  - Statistical power (21,087 participants)
  - Updated exposure assessment using data from 60+ follow-up years

Charge Q5f(i)

Cancer Dose-Response Assessment for Leukemia

- To ensure the best available science, EPA selected studies for dose-response analysis based on the following:
    1) Studies that used the full cohort data through 2009 and quantitative exposure data
    2) Inclusion of all male and female study participants: cohort size is 21,087 workers
    3) Used the updated exposure assessment from Macaluso (2004)
    4) The quality of the publication is rated High or Medium in the systematic review

Cancer Dose-Response Assessment for Leukemia

Reference	Statistically significant result?	Quality of the study in systematic review, rated High or Medium	Included data in the Follow-up period in 2009	Included all male and female study participants	Used updated exposure assessment
Sathiakumar, 2015	Significant (D-R, male only)	Medium	√		√
Sathiakumar, 2019	Significant (work years as exposure proxy)	Medium	√	√	√
Sathiakumar, 2021	**Significant (D-R)**	**Medium**	**√**	**√**	**√**
Valdez-Flores, 2022	Significant (D-R)	Low	√	√	√

Charge Q5f(i-ii)

Study and Model Selection for Leukemia IUR

Sathiakumar, 2021b was selected for leukemia lifetable analysis:

- Used the data from SBR cohort (US-Canadian styrene-butadiene rubber cohort study)
- Used the updated exposure assessment of the SBR cohort (US-Canadian styrene-butadiene rubber cohort study) (Macaluso, 2004)
- Male and female participants (21,087 men and women) were included
- The quality of the study in the systematic review is rated medium
- Provides dose-response relationship information

Statistical Model Options:	Lag Time (years)	β (Beta Coefficient)	Upper 95% Confidence Bound on β	Trend P Value
1. All person-time (untrimmed, including unexposed)	0	2.55E−04	4.57E−04	0.014
2. All person-time (untrimmed, including unexposed)	10	2.58E−04	4.78E−04	0.022
3. All person-time (untrimmed, including unexposed)	20	2.63E−04	5.31E−04	0.055
4. Exposed person-time (exclude unexposed)	0	2.50 E−04	4.73E−04	0.028
5. Exposure person time ≤95th percentile: Restricted cubic spline (RCS) Cox regression model (trim to restrict data)	0	9.94E−04	18E−04	0.016

Charge Q5f(ii-iii)

Study and Model Selection for Leukemia

Restricted cubic spline (RCS) Cox regression model

- At low exposure levels:
  - IUR represents the dose-response association at a lower exposure range; exposure-response curves at lower exposure levels can be improved after excluding ≥95% exposure person time.
- At high exposure levels:
  - Excluding ≥95% exposure person time can reduce the impact of exposure outliers.
- Model fitting performance:
  - Stronger exposure-response trends while excluding exposures above the 95th percentile.
- Better model fitting:
  - Showed more robust model fitting than other models.

Charge Q5f(ii)

IUR Derivation for Leukemia – Data in Lifetable

Data input

- Population statistics
  - U.S. age-specific all-cause mortality in 2019 among all race and gender groups
  - Leukemia-specific incidence from the Surveillance, Epidemiology, and End Results (SEER) 22
- Epidemiological data from the linear or log-linear model
  - Beta (β): an estimate of the increase in the outcome (e.g., leukemia incidence) that results from an increase of one unit of exposure to 1,3-butadiene
  - Upper 95% confidence bound (CB) on β
- Selection of Benchmark Response (BMR): usually 1% for cancer epidemiological data

Charge Q5f(ii-iii)

IUR Derivation for Leukemia – Data in Lifetable Analysis

- Data output
  - 95% lower confidence limit of the exposure concentration (LEC_{BMR}) that results in leukemia's extra risk (1%) after exposure to 1,3-butadiene
  - The selected exposure levels correspond to the specified level of extra risk, e.g., 1%.

- Other variables and values in the lifetable
  - Lifetable age span: 16-85 years
  - Lag time = 0 years
    - Various lag times (0, 10, 20 years) showed no significantly different impacts on β
    - CDC concluded the minimum latency of leukemia is 0.4 years

Charge Q5f(ii-iii)

IUR Derivation for Leukemia – Timeline of Modified IUR and Associated Changes

IUR and Associated Changes	Associated Document	Time
Initial, draft IUR was derived	<u>Initial IUR was described/presented in:</u> Sections 5.3 and 8 of the *07. Draft Human Health Hazard Assessment for 1,3-Butadiene*	Internal review process (August, 2024)
IUR was modified to assume exposure starts at age 16	<u>Modified IUR was described/presented in:</u> • Appendix F of 7. *Draft Human Health Hazard Assessment for 1,3-Butadiene* • Memorandum: *34. Corrected Lifetable Analyses for Leukemia and Bladder Cancer*	November 2024 (release date of draft RE package)
Text clarifications for cancer risk updates to the risk evaluation	<u>List of updates to Risk Evaluation document:</u> Memorandum: *37. Addendum to Draft Risk Evaluation and corrected Lifetable Memo for 1,3-Butadiene*	December 4, 2024

Charge Q5f(iv)

IUR Derivation for Leukemia – New Modification in Lifetable

A refined assumption and associated modifications were made in the lifetable:

- Assumption: Occupational exposure starts at 16 years old
  - Set to zero for exposure duration for ages 0 to 15 years in in the lifetable
  - Exposure duration starts at age 16 in the lifetable
  - Two unit risks, 'adult-exposure-only' unit risk and 'adult-based' unit risk, were derived

Note:

- **The modified IUR described in Appendix F in *Draft Human Health Hazard Assessment for 1,3-Butadiene* does not change the initial IUR from Table 8-3 in the same document.**
- **Neither occupational nor general population risk estimates in Section 5.3 of the *Draft Risk Evaluation for 1,3-Butadiene* are expected to change.**

Charge Q5f(iv)

IUR Derivation for Leukemia -- Calculation

- Data used for IUR derivation
  - Calculation of unit risk (UR)

$$UR = BMR/\ LEC_{BMR} \text{ per unit of exposure} = BMR_{01}/LEC_{01} = 0.01/LEC_{01}$$

  - **UR**: the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to 1,3-butadiene at a concentration of 1 ug/m^3 in air
  - **BMR**: benchmark response of an adverse effect; BMR is set as 1% for most cancers
  - **LEC_{BMR}**: 95% lower confidence limit of the exposure concentration associated with a 1% increased risk

- **Lifetime IUR (IUR)**: applies the ADAF to the 'adult-based' unit risk at 95 percent upper-bound to obtain the lifetime IUR
  - Mutagenic mode of action (MMOA) warrants application of Age-Dependent Adjustment Factors (ADAFs)
  - ADAF accounts for increased susceptibility to mutagens for children in the absence of data in the younger life stages

Charge Q5f(ii-iii)

IUR Derivation for Leukemia -- ADAF

Incorporation of ADAF for General Population Risk Estimation

Age[b]	ADAF Adjustment[a]	Adjusted Partial Life UR and General Population IUR
0 to <2	10×	0.0062 × 10 × (2/78) = 0.0016
2 to <16	3×	0.0062 × 3 × (14/78) = 0.0033
≥16	1×	0.0062 × 1 × (62/78) = 0.0049
0 to 78		**0.0098 per ppm (4.4E–06 per µg/m³)**

[a] ADAFs are applied based on the determination of a mutagenic MOA (Section 5.3) and in accordance with (U.S. EPA, 2005b).

[b] Adjusted IUR value is based on an assumption of 78 years lifetime (U.S. EPA, 2011).

Charge Q5f(iv)

IUR Derivation for Leukemia -- Results

- IUR for general population: 0.0098 per ppm
- UR for workers: 0.0049 per ppm

	Adult-exposure-only unit risk at 16+ years old (62 years)	Adult-based unit risk (78 years) (for general population)	**IUR** (general population)	Unit Risk for workers (62 years)
Updated calculation (exposure starting at 16 years)	0.0049 per ppm	0.0062 per ppm	**0.0098 per ppm**	0.0049 per ppm

Key parameters in lifetable analysis: β for 95% UB = 0.0018; Lag time = 0 years; LEC_{01} at 5% LB = 2.046 ppm

Charge Q5f(i-iv)

Weight of Evidence for Bladder Cancer

- Epidemiological studies
  - 2 out of 7 publications showed a significant, positive association
  - Same US-Canadian styrene-butadiene rubber cohort
  - Bladder cancer case numbers were small in the cohort
  - Smoking - a risk factor for bladder cancer - was not adjusted for in the dose-response model
    - ➢ However, Blair et al., (2007) showed that tobacco-adjusted relative risks rarely differ appreciably from unadjusted estimates for studies of occupational exposure and lung cancer
- Animal toxicology
  - No increased incidence of bladder cancer in mice or rats
- Mechanistic evidence
  - MMOA analysis based on leukemia, however mutagenicity may also apply to other tissues
  - No mechanistic studies were found for bladder cancer

Cancer Type	Human	Animal	Mechanistic
Bladder	Moderate	Indeterminate	Slight

Charge Q5f(ii)

Study and Model Selection for Bladder Cancer

- Sathiakumar, 2021a selected for bladder cancer lifetable analysis:
  - Same consideration as leukemia
- Model selection
  - "Exposed person-time (exclude unexposed)" (Model 4) was selected

Statistical Model	Lag Time (years)	β (Beta-Coefficient)	Upper 95% Confidence Bound on β	Trend P-Value
1. All person-time (untrimmed, including unexposed)	0	3.84E−04	6.12E−04	0.001
2. All person-time (untrimmed, including unexposed)	10	3.87E−04	6.21E−04	0.001
3. All person-time (untrimmed, including unexposed)	20	4.22E−04	6.80E−04	0.001
4. Exposed person-time (exclude unexposed)	0	3.50E−04	5.95E−04	0.005
5. Exposure person time <=95th percentile: Restricted cubic spline (RCS) Cox regression model (trim to restrict data)	0	4.72E−04	13.79E−04	0.308

Charge Q5f(ii)

Study and Model Selection for Bladder Cancer

Bladder cancer latency

- In the initial lifetable analysis, lag time was set to 20 years based on the evidence in the literature.
- In the modified lifetable analysis, lag time was set to 0 years.
  - The model results used for lifetable incorporated lag of 0 years.
  - The modeling of different lag times in exposure showed little effect on the beta coefficient.

Charge Q5f(ii)

IUR Derivation for Bladder Cancer

- The lifetable analysis and unit risk (UR)/IUR derivation for bladder cancer use the same method as that for leukemia.
- General Population IUR: 0.0045 per ppm; Chronic Occupational UR: 0.0022 per ppm.
- *Due to uncertainty in the weight of evidence, UR/IUR for bladder cancer were not combined with UR/IUR for leukemia, respectively, and were not used for risk estimation*.

	Adult-exposure-only unit risk at 16+ years old (62 years)	Adult-based unit risk (78 years) (for gen-pop)	IUR (general population)	Unit Risk for worker
Updated calculation (exposure starting at 16 years)	0.0022 per ppm	0.0028 per ppm	0.0045 per ppm	0.0022 per ppm

Key parameters in lifetable analysis: β for 95% UB = 0.000556; Lag time = 0 years; LEC_{01} at 5% LB = 4.46 ppm

Charge Q5f(ii-iii)

Conclusion for 1,3-butadiene for Cancer Outcomes

- EPA OPPT updated the 1,3-butadiene unit risk/IUR using the best available science from epidemiological studies during 1996-2022
- 1,3-Butadiene is considered "carcinogenic to humans"
  - Strong epidemiological evidence of leukemia
  - Moderate epidemiological evidence and indeterminate animal toxicological evidence of bladder cancer
- Proposed IUR/UR for leukemia
  - For general population (IUR): 0.0098 per ppm; for workers (UR): 0.0049 per ppm
- Calculated IUR/UR for bladder cancer
  - For general population (IUR): 0.0045 per ppm; for workers (UR): 0.0022 per ppm
- More evidence may be needed to support bladder cancer risk
  - Uncertainty in the weight of evidence
  - Bladder cancer case numbers were small in the cohort
  - Smoking was not adjusted for in the dose-response association in statistical models

Charge Q5e,f

EPA United States Environmental Protection Agency

Thank you for your attention

EPA United States Environmental Protection Agency

GENERAL POPULATION EXPOSURE ASSESSMENT AND ANALYSIS

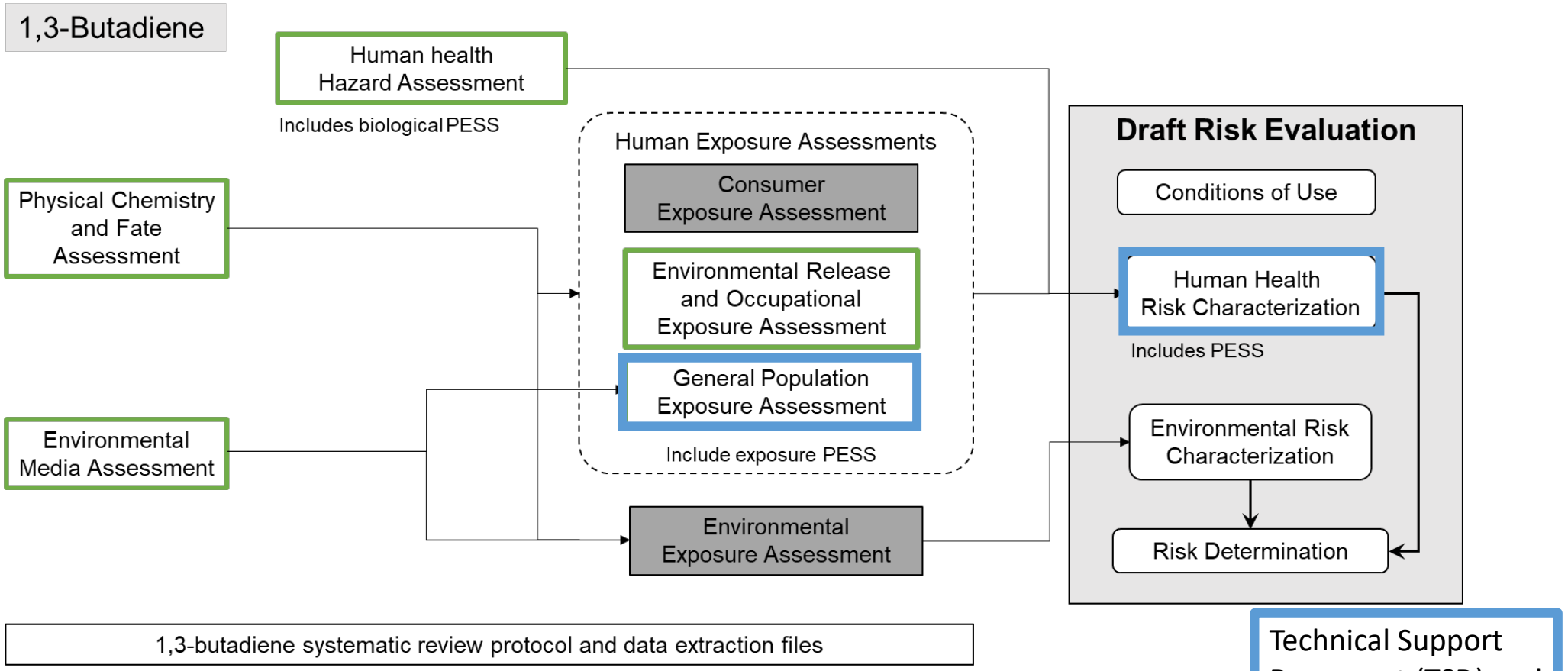
Kiet Ly, M.P.H., OCSPP/OPPT

Charge Q2

General Population Exposure Assessment and Analysis

- *Draft General Population Exposure Assessment*
- *Draft 1,3-Butadiene Risk Assessment:*
  - ***Section 5.3.4*:** Risk Estimates for General Population Exposed to Environmental Releases
- *Support Document*: Draft IIOAC TRI 2016 to 2021 Exposure and Risk Analysis
- *Support Document*: Draft HEM TRI 2016 to 2021 Exposure and Risk Analysis
- *Support Document*: Draft Environmental Release and Occupational Exposure Assessment
- *Support Document:* Draft Human Health Hazard Assessment for 1,3-Butadiene
- *Support Document*: Draft Environmental Media Concentrations
- *Support Document*: Draft AMTIC Monitoring Data 2016 to 2021

Charge Questions	Reference Documents
Charge Question 2 (General Population Exposure Assessment)	Draft General Population Exposure Assessment for 1,3-Butadiene https://www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0017



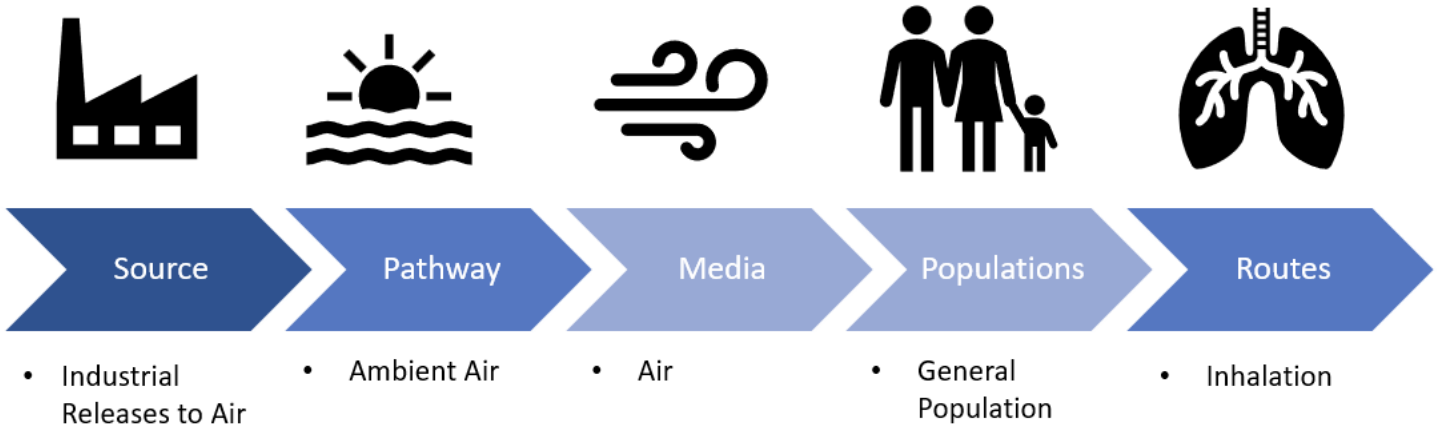
TSDs outlined in **green**; shaded boxes indicate qualitative narrative in main RE without separate TSD

Figure 2-6 in Draft 1,3-Butadiene Risk Evaluation

Charge Q2

Technical Support Document (TSD) and Sections of Risk Evaluation Related to this Charge

TSCA RISK ASSESSMENT CONSIDERATIONS FOR GENERAL POPULATION



Exposure Pathway	Analysis	Reasoning for Analysis
Ambient Air	• Quantitative analysis of inhalation of 1,3-butadiene in air resulting from facility releases	• 1,3-Butadiene expected to be in air and to be present in gaseous phase • Not expected to undergo air deposition or long-range transport due to relatively short half-life (0.76 to 9 hours) and low K_{OA} • Monitoring studies showing 1,3-butadiene in air (US and non-US) • EPA AMTIC AMA monitoring database 2016-2021 detecting 1,3-butadeiene in air • Known air releases from TSCA facilities

Charge Q2

GENERAL POPULATION EXPOSURE AIR PATHWAY

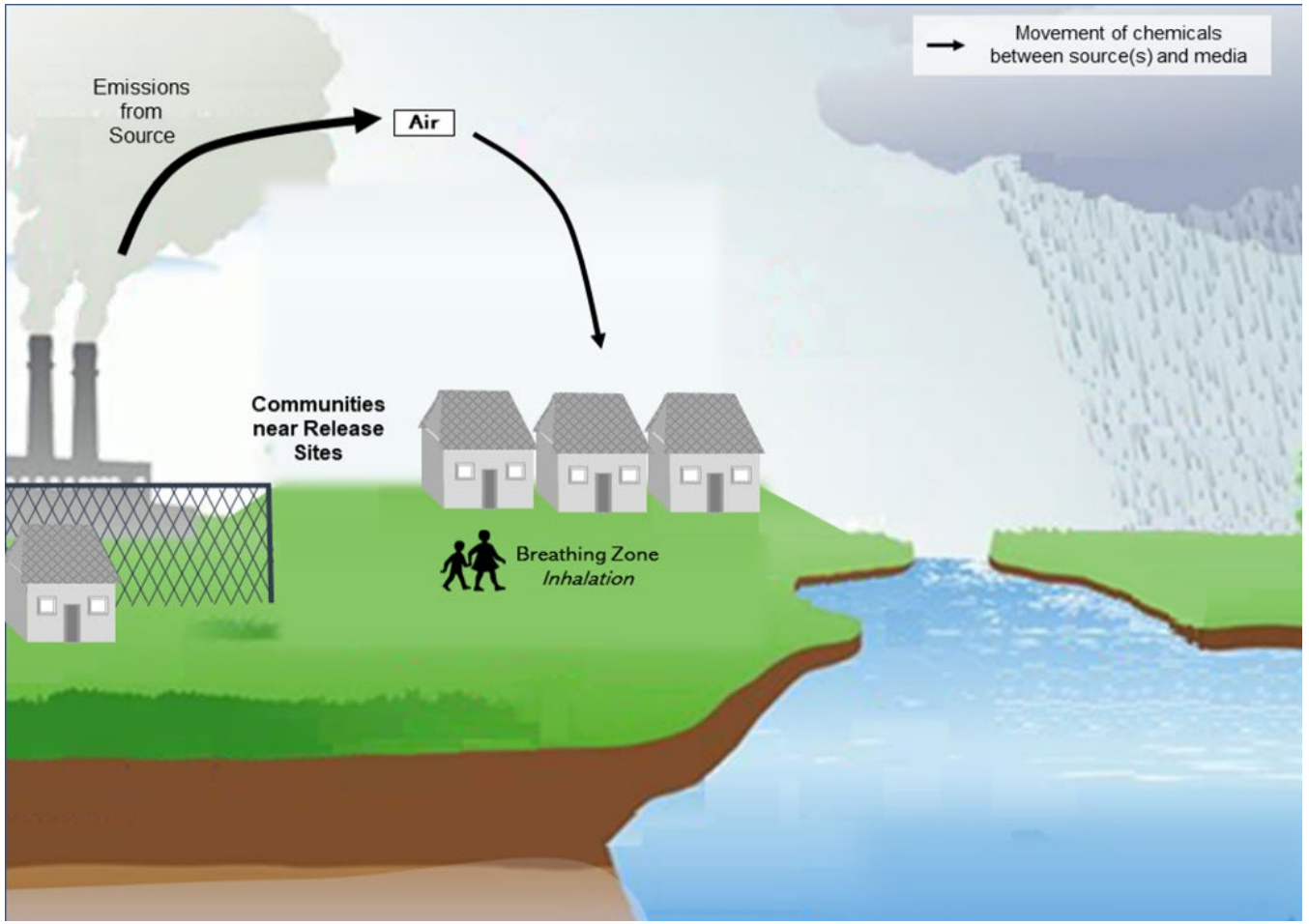


Figure 2-1 in *Draft General Population Exposure Assessment*

Charge Q2

GENERAL POPULATION EXPOSURE TIERED APPROACH - INTEGRATED INDOOR-OUTDOOR AIR CALCULATOR

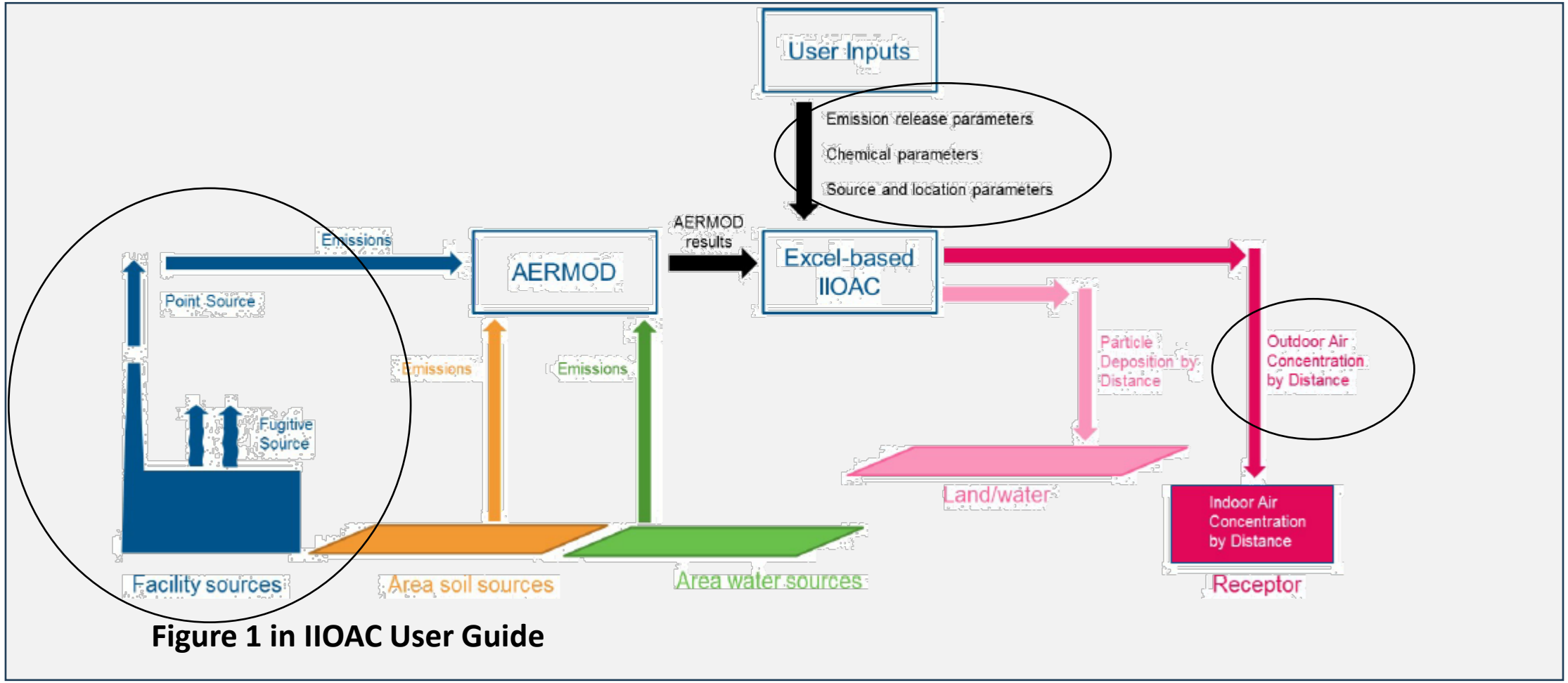


Figure 1 in IIOAC User Guide

Charge Q2 i.

GENERAL POPULATION EXPOSURE TIERED APPROACH - IIOAC

- EPA used a tiered approach for general population exposure starting with the Integrated Indoor/Outdoor Air Calculator (IIOAC)
  - Release Data Set
    - Toxic Release Inventory (TRI) Data 2016 to 2021
    - 225 reporting facilities
  - Release Type
    - Stack and fugitive releases modeled separately, then combined
  - Release Scenario and Pattern
    - Operating 365 days per year
    - 24 hours/day
    - Consecutive
  - Meteorological Station
    - South (Coastal): Surface and Upper Air Stations at Lake Charles, Louisiana
  - Land Use
    - Rural

Stack Release Parameters	Value	Fugitive Release Parameters	Value
Stack height (m)	10	Length (m)	10
Stack diameter (m)	2	Width (m)	10
Exit velocity (m/sec)	5	Angle (°)	0
Exit temperature (K)	300	Release height (m)	3.05

Table 2-1 in Draft General Population Exposure Assessment

Charge Q2i and iii.

IIOAC MODELED CONCENTRATIONS AND EXPOSURE

- IIOAC models 95th percentile and mean ambient air concentrations at 100, 100 to 1,000 and 1,000 m from releasing facilities
- 95th percentile results for ambient modeled concentrations across all facilities, reporting years, and modeled distances ranged from 0 to 109.5 µg/m^3
- EPA assumed that individuals are exposed to ambient air concentrations 24 hours a day, 365 days a year over a lifetime

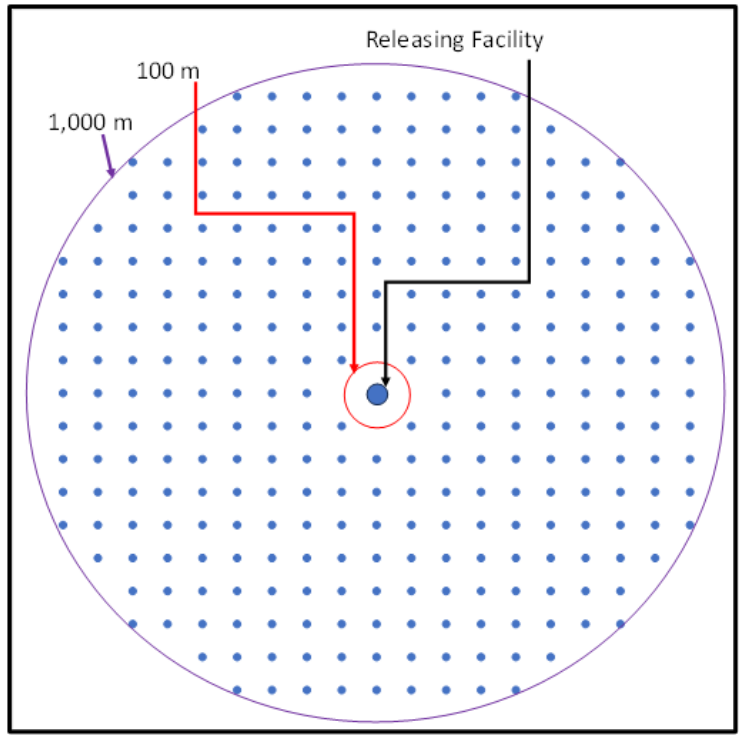


Figure illustrating finite distance rings and area buffer modeled in IIOAC

SCREENING LEVEL NON-CANCER RISK ESTIMATES

- Screening Non-Cancer Risk Estimates
  - Margin of Exposures (MOEs) were calculated using chronic Human Equivalent Concentration (HEC) and the 95th percentile (and mean) modeled concentrations for each TRI facility
    - HEC = 2.5 ppm or 5,500 µg/m^3
    - MOE Benchmark = 30
    - Draft Human Health Hazard Assessment for 1,3-Butadiene

$$Margin\ of\ Exposure\ (MOE) = \frac{Human\ Equivalent\ Concentration\ (HEC)}{Modeled\ Exposure\ Concentration}$$

  - No resulting MOEs were below the chronic non-cancer benchmark
    - i.e., MOEs > 30 for all 225 form R facility releases reported in TRI 2016 to 2021
- Based on the above results, further refinement was not conducted

Charge Q2 i.

SCREENING LEVEL CANCER RISK ESTIMATES

- Screening Cancer Risk Estimates
  - Lifetime excess cancer risk is calculated using the inhalation unit risk (IUR) and modeled concentrations (95th percentile and mean) for each TRI facility
    - IUR = 4.4 x 10^{-6} per µg/m^3
    - Cancer Risk Benchmark = 1 x 10^{-6} to 1 x 10^{-4} (1 in a million to 1 in 10,000)
    - Draft Human Health Hazard Assessment for 1,3-Butadiene

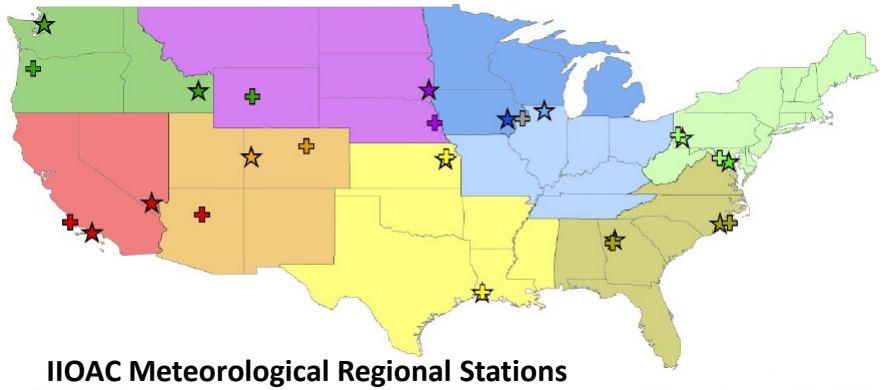
$$Lifetime\ Excess\ Cancer\ Risk\ = Modeled\ Exposure\ Concentration\ \times\ Inhalation\ Unit\ Risk\ (IUR)$$

  - Facilities with screening level cancer risk above 1 in a million
    - 132 facilities based on 95th percentile IIOAC modeled concentrations
    - 128 facilities based on mean IIOAC modeled concentration
- Based on the above results, the ambient air modeling approach was refined

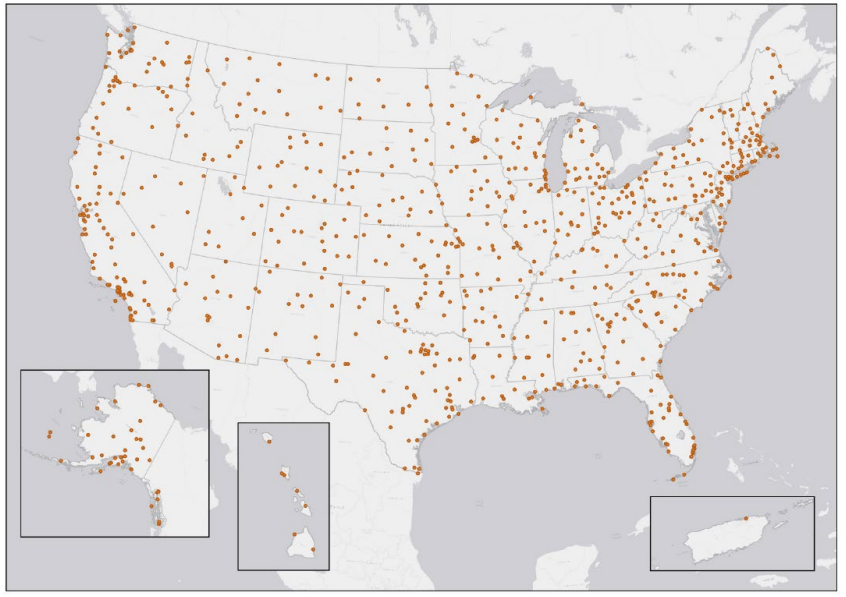
Charge Q2 i.

GENERAL POPULATION EXPOSURE
TIERED APPROACH – HUMAN EXPOSURE MODEL

- Based on these results, EPA proceeded with a refined analysis using the Human Exposure Model (HEM)
  - AERMOD dispersion model
  - Localized regional data for meteorology and land use
  - Modified user inputs and parameters (if available)
  - HEM models concentrations at further distances from releasing facilities
  - HEM models and estimates risks at census blocks



IIOAC Meteorological Regional Stations



HEM Meteorological Stations

Charge Q2 ii.

GENERAL POPULATION EXPOSURE HUMAN EXPOSURE MODEL – TOXIC RELEASE INVENTORY DATA

- EPA further refined modeling for general population exposure starting with the Human Exposure Model (HEM)
  - Release Data Set
    - Toxic Release Inventory (TRI) Data 2016 to 2021
    - 225 reporting facilities
  - Release Type
    - Stack and fugitive releases modeled separately, then combined
  - Release Scenario and Pattern
    - Operating 250-350 days per year as reported to TRI
    - 24 hours/day
    - Patterned releases
  - Meteorological and Land Use
    - Localized meteorological and census data

Stack Release Parameters	Value	Fugitive Release Parameters	Value
Stack height (m)	10	Length (m)	10
Stack diameter (m)	2	Width (m)	10
Exit velocity (m/sec)	5	Angle (°)	0
Exit temperature (K)	300	Release height (m)	3.05

Table 2-2 in Draft General Population Exposure Assessment

Days per Year of Emissions	Release Pattern
250	Monday to Friday, except no Fridays in January to March Equals 247–249 days/year, depending on the year Emission factor when emissions on = 1.473
300	Monday to Saturday, except no Saturdays in January to March. Equals 200–201 days/year, depending on the year Emission factor when emissions on = 1.217
350	All days, except no Sundays in January to April. Equals 347–349 days/year, depending on the year Emission factor when emissions on = 1.05

Table_Apx B-4 in Draft General Population Exposure Assessment

Charge Q2 ii. and iii.

GENERAL POPULATION EXPOSURE TIERED APPROACH - HEM

- **Two sets of modeling results**
  - Radial Distances
    - Models 95th, 50th and 10th percentile concentrations at each distance from 10 to 50,000 meters

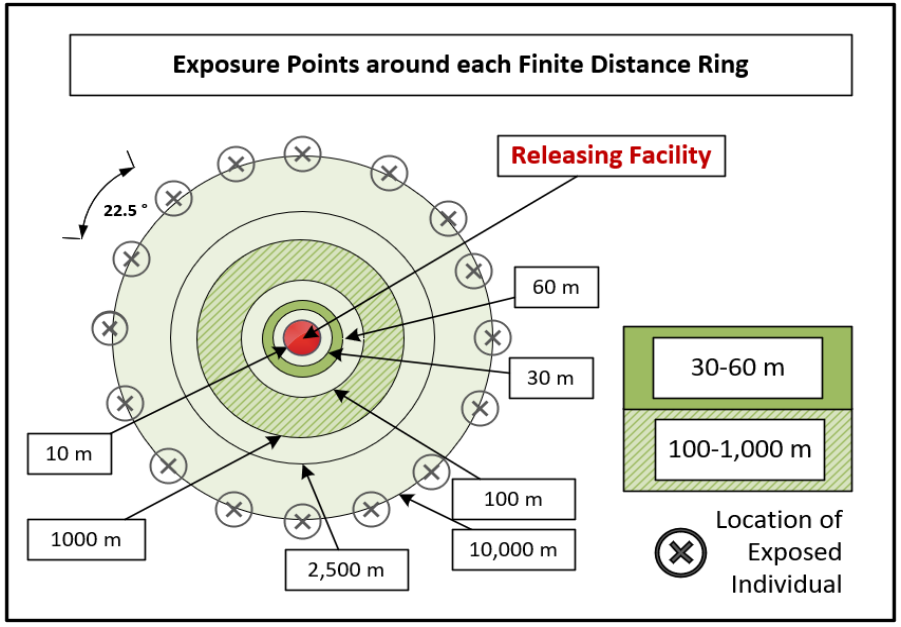


Figure illustrating radial distances modeled in HEM

  - Census Blocks
    - Models a single concentration and risk estimate at the center of census blocks within 50,000 meters from releasing facilities

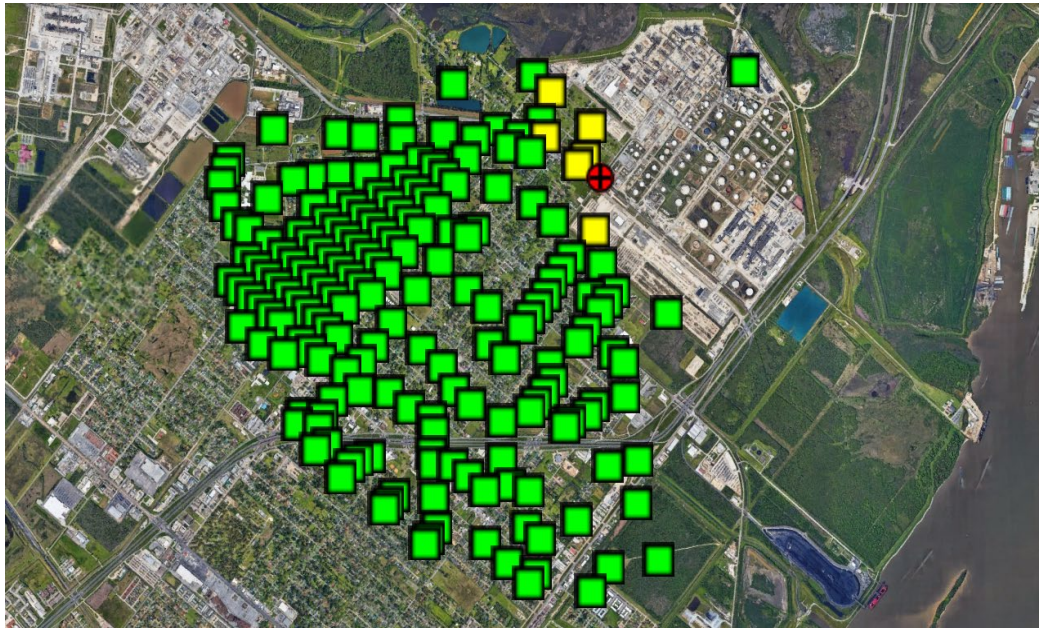


Figure illustrating census blocks modeled in HEM

Green squares = modeled risks less than 20 in a million
Yellow squares = modeled risks between 20 to 100 in a million

Charge Q2 ii.

HEM – TRI AND NEI DATA COMPARISON

- EPA conducted a targeted sensitivity screen using National Emissions Inventory (NEI) 2017 and 2020 release data
- 1,3-Butadiene TRI and NEI Risk Estimate Comparison Analysis
- NEI data reports facility-specific parameters

Input	TRI Dataset	NEI Dataset
Release coordinates	One per facility (Facility-wide)	Can be multiple per facility (Emission Unit-specific)
Emission days/year	250-350	As reported (1-366)
Stack		
Height (m)	10*	As reported, or 10
Diameter (m)	2*	As reported, or 2
Exit Velocity (m/sec)	5*	As reported, or 5
Exit Temperature (K)	300*	As reported, or 300
Fugitive		
Length (m)	10	As reported, or 10
Width (m)	10	As reported, or 10
Angle (˚)	0*	As reported, or 0
Release height (m)	3.05*	As reported, or 3.05

*TRI dataset does not provide values for stack and fugitive parameters; EPA uses default values from IIOAC user guide.

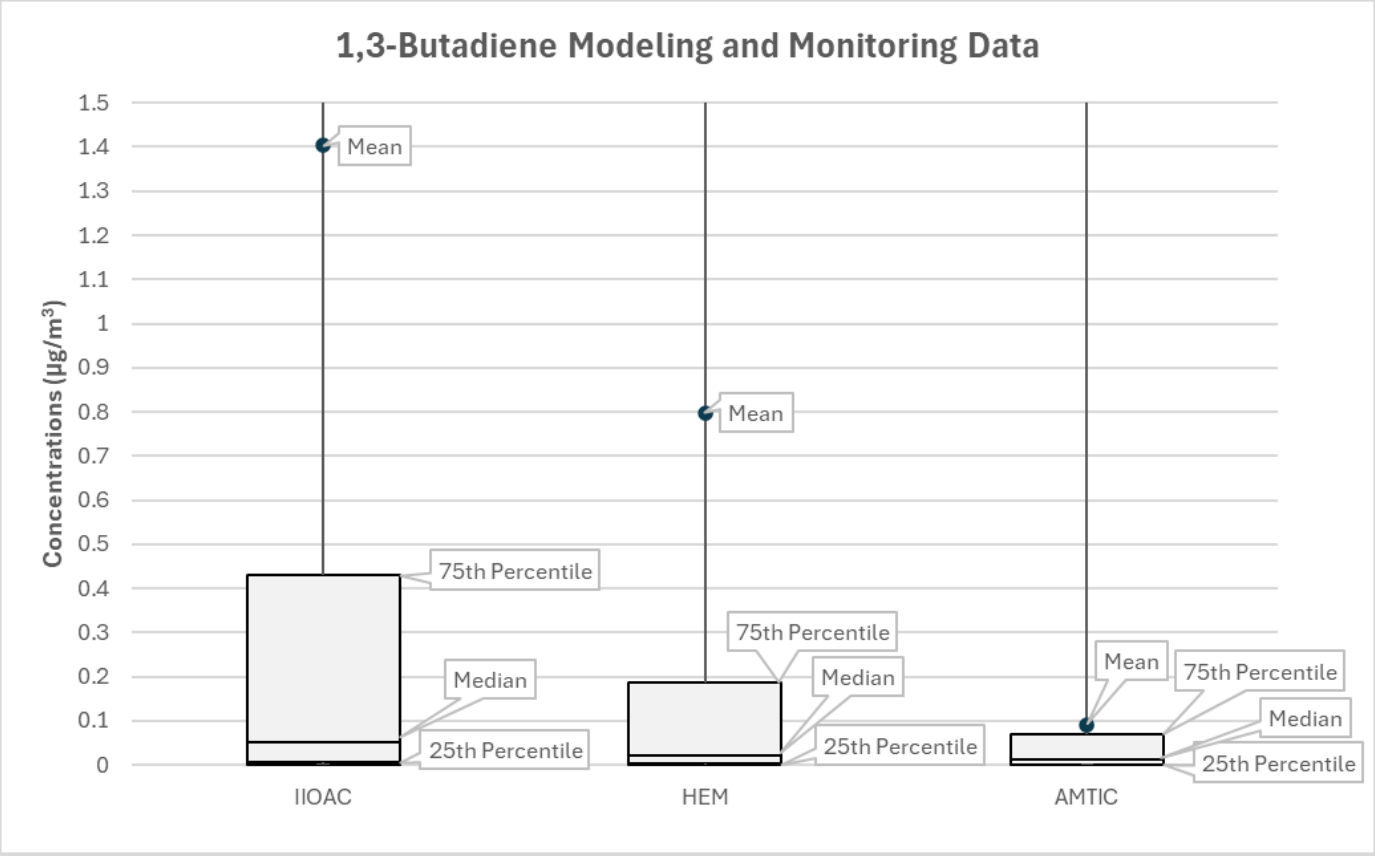
Charge Q2 ii. and iii.

EPA United States Environmental Protection Agency

MONITORING DATA

- EPA evaluated the Ambient Monitoring Technology Information Center Air Monitoring Archive (AMTIC AMA) monitoring data for samples collected from January 2016 through December 2021
- The 1,3-butadiene AMTIC AMA monitoring data included over 55,000 24-hour sampling entries from 12 monitoring programs covering 34 states and 331 census tracts
- 24-Hour monitored concentrations from the AMTIC archive ranged from 0.0 to 122.8 $\mu g/m^3$
  - Highest monitored value recorded along Gulf coast in Port Neches, Texas
- Monitoring data supports a quantitative assessment of ambient air pathway for general population exposure
- See Draft Environmental Media Concentrations for 1,3-Butadiene for more details

MODELING AND MONITORING DATA



	Concentrations(µg/m3)		
	IIOAC[a]	HEM[b]	AMTIC[c]
Maximum	100.286	80.052	122.834
Mean	1.404	0.798	0.091
75th	0.429	0.188	0.071
Median	0.052	0.023	0.013
25th	0.005	0.003	0.000
Minimum	0.000	0.000	0.000

[a]Modeling data presented based on IIOAC mean concentrations at 100 to 1000 meters meters (2016-2021 TRI Release Data)
[b]Modeling data presented based on HEM 50th percentile concentrations at 100 to 1000 meters (2016-2021 TRI Release Data)
[c]Monitoring data presented based on 24-hour reported values

Charge Q2 iv.

CONCLUSION AND KEY POINTS

- EPA used a tiered approach to assess general population exposure by:
  - Using IIOAC to model ambient air concentrations based on TRI 2016 to 2021 reporting years
    - 100 to 1,000 meters away from facility releases
    - Due to screening-risk estimates being above the benchmark, EPA did not refine analyses for non-cancer risks
    - Due to screening-level risk estimates being above 1 in a million, analyses were further refined for cancer risks
  - Using HEM to model ambient air concentrations based on TRI (2016 to 2021) and NEI (2017 and 2020) reporting years
    - 10 to 50,000 meters away from facility releases
    - Census blocks within 3,000 meters and up to 50,000 meters away from facility releases
      - Aggregated risk estimates

Charge Q2

CONCLUSION AND KEY POINTS

- Comparing modeled concentrations and monitoring data show that concentrations are within the same order of magnitude, but the monitored data distribution is lower
- EPA acknowledges that NEI 2017 and 2020 release data provides refinement to exposure estimates and is evaluating data for inclusion in the final risk evaluation
- See Draft General Population Assessment for 1,3-Butadiene and Draft Risk Evaluation for 1,3-Butadiene for more details

EPA United States Environmental Protection Agency

1,3-BUTADIENE CONSUMER EXPOSURE ASSESSMENT

Kiet Ly, M.P.H., OCSPP/OPPT

Charge Q3

EPA United States Environmental Protection Agency

CONSUMER EXPOSURE QUALITATIVE ASSESSMENT

- Use of plastic and rubber products, including synthetic rubbers, were identified as consumer conditions of use for 1,3-butadiene
- EPA determined that 1,3-butadiene is a monomer used to created polymers for consumer products
  - Polymers include but are not limited to, acrylonitrile-butadiene-styrene (ABS) resins and styrene-butadiene rubber (SBR)
- These polymer-based products are considered stable and are not expected to degrade or depolymerize into the 1,3-butadiene monomer
- Residual 1,3-butadiene concentrations in polymers are very low and often not detectable

EPA conducted a qualitative assessment for consumer exposure and does not expect exposures to the 1,3-butadiene monomer

Charge Q3

EPA United States Environmental Protection Agency

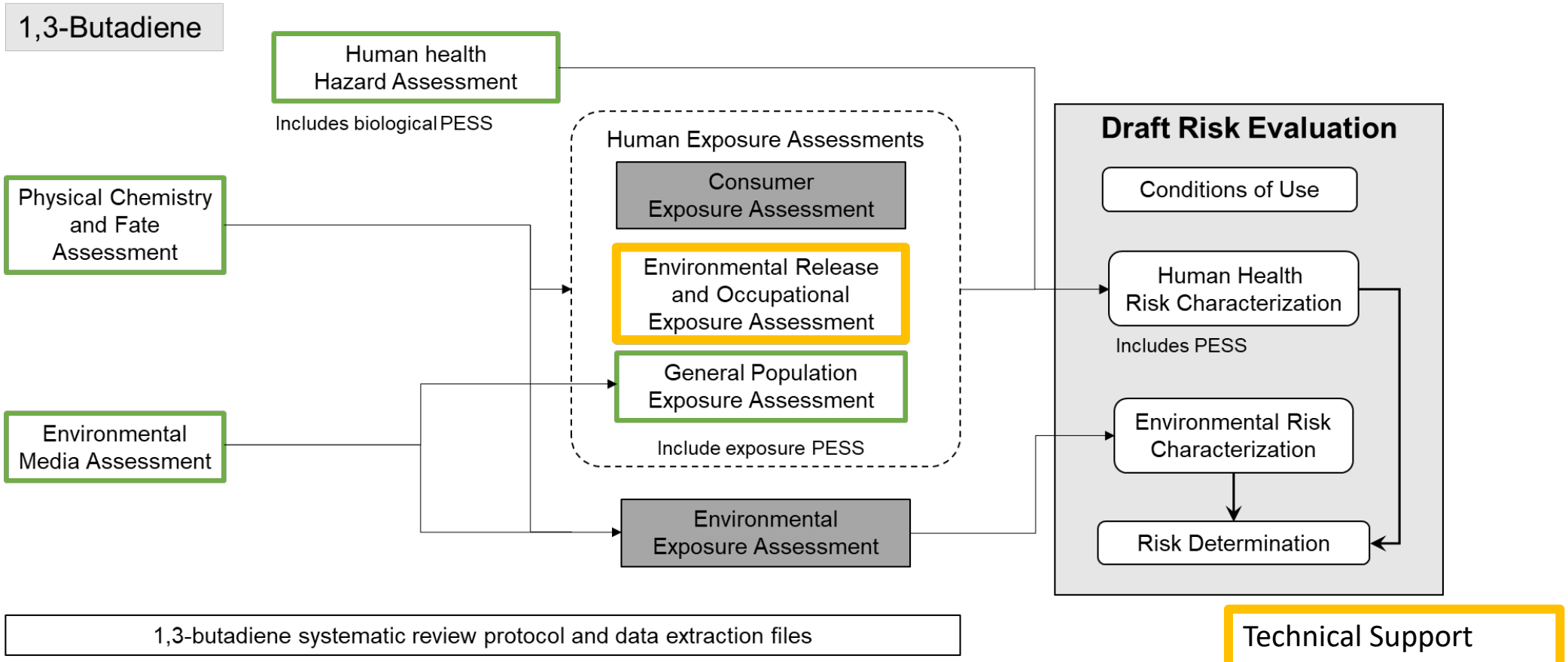
Thank you for your attention

EPA United States Environmental Protection Agency

1,3-BUTADIENE OCCUPATIONAL EXPOSURE ASSESSMENT

Catherine Taylor, B.S., OCSPP/OPPT

Charge Questions	Reference Documents
Charge Question 4 (Occupational Exposure Assessment)	Draft Environmental Release and Occupational Exposure Assessment for 1,3-Butadiene www.regulations.gov/document/EPA-HQ-OPPT-2024-0425-0015



TSDs outlined in **green**; shaded boxes indicate qualitative narrative in main RE without separate TSD

Technical Support Document (TSD) and Sections of Risk Evaluation Related to this Charge

1,3-BUTADIENE OCCUPATIONAL MONITORING DATA

- Within the 1,3-butadiene risk evaluation, monitoring data was used to estimate occupational exposure for all quantitatively assessed conditions of use (COUs)
- Occupational monitoring data was obtained from multiple sources
  - American Chemistry Council's (ACC's) *Analysis of 1,3-Butadiene Industrial Hygiene Data*
    - Includes a compilation and analyses of 5,676 full-shift personal breathing zone (PBZ) samples for workers and occupational non-users (ONUs) collected from 47 consortium member facilities from 2010 to 2019
    - Inhalation exposure data was provided for a variety of Similar Exposure Groups (SEGs)
  - U.S. Tire Manufacturers Association's (USTMA) public comment and Lee et al.'s journal article *Work environments and exposure to hazardous substances in Korean tire manufacturing*, obtained through systematic review
    - Includes 102 full-shift PBZ samples for workers from several facilities in 2020 and 2012 respectively
  - Occupational Safety and Health Administration's Chemical Exposure Heath Data (OSHA CEHD)
    - Includes 43 full-shift PBZ samples for workers from five facilities collected between 2000 to 2016

NON-DETECTS IN 1,3-BUTADIENE OCCUPATIONAL MONITORING DATA

- Non-detects occur when a sample is below the limit of detection (LOD)
  - LOD is the lowest concentration of a chemical that can reliably be detected in a sample, and depends on the sampling method and flow rate
- In the ACC dataset, 86.8% of the full-shift samples were below the LOD, which ranged from 0.0008 ppm to 1.3 ppm
  - The percent of data points below the LOD varied for the different SEGs
  - Only one full-shift SEG dataset was 100% non-detects, the remaining datasets contain at least one data point above the limit of detection
- In *USTMA, 2020* and *Lee et al., 2012,* 64.6% of the full-shift samples were below the LOD, which ranged from 0.008 ppm to 0.95 ppm
- In OSHA CEHD, 100% of the data was below the LOD of 0.090 ppm

APPROACH FOR HANDLING NON-DETECTS

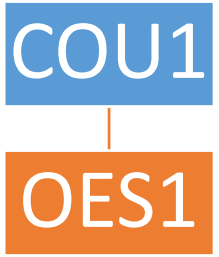
- Substitution method was used where non-detect values were substituted with the sample's LOD divided by two, or the square root of two
  - Choice of substitution method (LOD divided by two, or the square root of two) depended on the geometric standard deviation for each dataset

- In the case of a dataset with 100% non-detects, the LOD divided by two is assumed to be the median of exposure, and the LOD is assumed to be a conservative high-end exposure

- Substitution method is described in EPA's Guidelines for Statistical Analysis of Occupational Exposure Data (EPA, 1994)

IDENTIFYING AND DESCRIBING OCCUPATIONAL EXPOSURE SCENARIOS

- In a chemical risk evaluation, conditions of use (COUs) are the circumstances under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of
- Occupational exposure scenarios (OESs) are used to characterize a COU's release and exposure potential, and they allow grouping of similar activities across COUs
- Each COU is mapped to an OES using one of three approaches:



One COU can map to one OES (*e.g.*, the Manufacture COU is its own OES).

Multiple COUs can be grouped into one OES (*e.g.*, Importing and Intermediate in: wholesale and retail trade were both assessed under the "repackaging" OES").

One COUs can be broken into multiple OES (*e.g.*, Waste handling, treatment, and disposal and Recycling).

- 15 OESs were identified for 1,3-butadiene's 28 COUs

1,3-BUTADIENE OCCUPATIONAL MONITORING DATA

- The 1,3-butadiene risk evaluation used monitoring data to quantitatively assess OESs
- ACC's *Analysis of 1,3-Butadiene Industrial Hygiene Data*
  - Provided inhalation data for a variety of SEGs
  - Routine, nonroutine, and turnaround operations are captured for many tasks
  - Data rated as "high" quality per EPA data quality ratings for occupational exposure
- Seven of 1,3-butadiene's 11 OES were assessed using data from the ACC report. Of these seven:
  - Three OES had directly applicable data
  - For four OES, data of specific tasks and job descriptions were used as analogous

ANALOGOUS MONITORING DATA

- Analogous data are data that are of the same chemical, but for a different yet similar OES
- In some cases, no directly applicable data were found and monitoring data from similar expected tasks were used as analogous
- Understanding analogous data
  - The same tasks done at two different types of facilities may not align perfectly
  - When using task-based data as analogous data, it may be assumed that the single task such as loading/unloading at a manufacturing site is occurring throughout the day at a repackaging site
  - Alternative methods include directly applicable surrogate data from other chemicals, and modeling

In the absence of directly applicable data, use of monitoring data from the same or similar tasks as analogous data, even if the type of facility may vary, provides the best available estimate for exposure

DERMAL EXPOSURE TO 1,3-BUTADIENE

- The goal of an occupational exposure assessment is to estimate typical exposures that a worker or ONU may encounter
- In the case of 1,3-butadiene, dermal exposure was qualitatively assessed
  - 1,3-Butadiene is a volatile chemical, and is a gas at room temperature
  - 1,3-Butadiene is transported in a liquefied form by condensing the gaseous form under high pressure
  - Rapid evaporation of a liquid from a pressurized system will likely cause frostbite if it contacts the skin
  - Due to this severe hazard, robust personal protective equipment (PPE) is typically required where such an exposure is possible, so dermal exposure would not regularly occur
- From *Chemical Engineering Branch manual for the preparation of engineering assessments (1991):*
  - Qualitative assessment is appropriate for dermal exposure to gases
  - Negligible contact assumed in cases of corrosivity and high temperatures
- These principles were applied to the 1,3-butadiene occupational assessment

Due to the physical and chemical properties of 1,3-butadiene, EPA conducted a qualitative assessment of occupational dermal exposure.

EPA United States Environmental Protection Agency

Thank you for your attention

EPA United States Environmental Protection Agency

RISK CHARACTERIZATION PRINCIPLES

Kiet Ly, M.P.H., OCSPP/OPPT

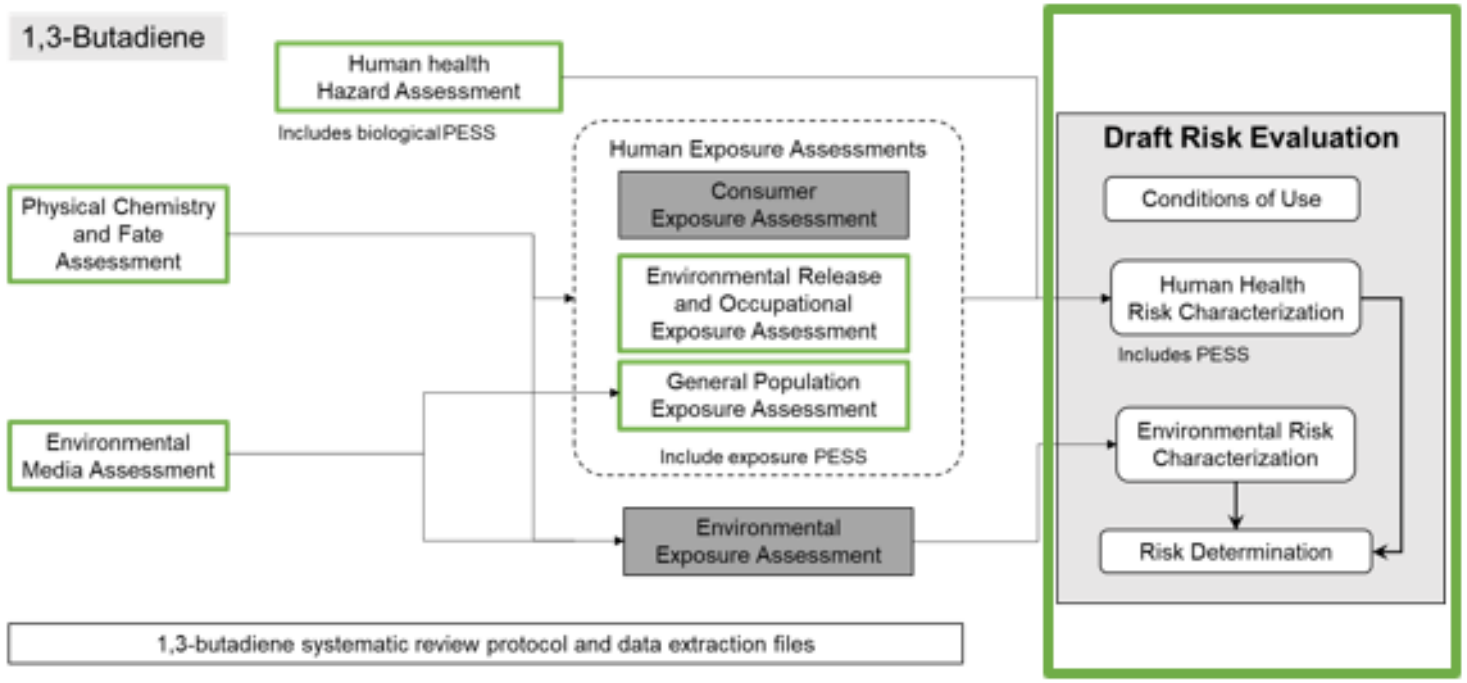
Charge Q6

RISK CHARACTERIZATION PRINCIPLES

[EPA Risk Characterization Handbook]

- **T**ransparency
- **C**larity
- **C**onsistency
- **R**easonableness

1,3-BUTADIENE DOCUMENT MAP



Charge Q6

EPA United States Environmental Protection Agency

Thank you for your attention