CHARGE to the TOXIC SUBSTANCES CONTROL ACT (TSCA) SCIENCE ADVISORY COMMITTEE ON CHEMICALS (SACC)

Peer Review of 2024 Draft Risk Evaluation for 1,3-Butadiene

BACKGROUND:

1,3-Butadiene (CASRN 106-99-0) is a volatile, colorless gas with a total U.S. production volume between 1 and 5 billion pounds. 1,3-Butadiene is used primarily as a chemical intermediate and as a monomer in the manufacture of polymers such as synthetic rubbers and elastomers. Workers may be exposed to 1,3-butadiene when making these products or otherwise using 1,3-butadiene in the workplace. When it is manufactured or used to make products, 1,3-butadiene is mainly released into the air due to its volatility, with relatively small releases to land or water. If released into land or water, 1,3-butadiene will quickly volatilize from land and water surfaces. 1,3-Butadiene in the air will photodegrade within a few hours by reacting with hydroxyl or nitrate radicals in the atmosphere. Additional sources of 1,3-butadiene exposure come from vehicle exhaust, tobacco smoke, burning wood and forest fires. Inhalation is the predominant route for human exposures and 1,3-butadiene risk has not been quantified by The U.S. Environmental Protection Agency (EPA or the Agency) for any other routes of exposure.

In the draft risk evaluation, EPA quantified risks resulting from exposure to 1,3-butadiene from facilities that use, manufacture, or process 1,3-butadiene under industrial and/or commercial conditions of use (COUs) subject to the Toxic Substances Control Act (TSCA), and the products resulting from such manufacture and processing. Human or environmental exposure to 1,3-butadiene from other sources (*e.g.*, vehicle exhaust, tobacco smoke, woodburning, etc.) were not quantitatively evaluated for risk characterization by EPA in reaching its preliminary determination of unreasonable risk of injury to human health.

EPA quantitatively evaluated hazards via the inhalation route. Inhalation hazards were assessed through systematic review of reasonably available evidence, which included human epidemiology, laboratory animal toxicology, toxicokinetics, and mechanistic data (including *in vitro* studies). EPA performed dose-response analysis for multiple non-cancer endpoints under the hazard domains of developmental toxicity from gestational exposure, male reproductive and developmental toxicity, and hematological toxicity. Decreased fetal weight was selected as the most robust and sensitive non-cancer endpoint for use in risk characterization (POD = 2.5 ppm or 5500 µg/m^3). EPA determined that 1,3-butadiene is carcinogenic to humans, with robust evidence across all evidence streams for lymphohematopoietic cancers, and the weight of scientific evidence supports a mutagenic mode of action for lymphohematopoietic cancers. EPA derived an IUR of 4.4×10^{-6} µg/m^3 or 0.0098 per ppm.

EPA evaluated the risks to people from being exposed to 1,3-butadiene at work and outdoors. In its human health evaluation, the Agency used a combination of screening-level and more refined approaches to assess how people might be exposed to 1,3-butadiene through inhalation.

The Agency has evaluated risks posed by 1,3-butadiene to human health and environment under TSCA, as presented in the *Draft Risk Evaluation for 1,3-Butadiene* (U.S. EPA, 2024f). The Agency is requesting peer review by the TSCA Science Advisory Committee on Chemicals (SACC) of the *Draft Risk Evaluation for 1,3-Butadiene*. EPA is specifically seeking SACC review of its analyses and

methodologies relevant to hazard and exposure methodologies that have not been previously peer reviewed.

Once EPA receives comment and input from peer review and public comment, revisions will be made and the Agency will finalize its assessments and risk determination (*i.e.*, risk evaluation) for 1,3-butadiene. By taking the 1,3-butadiene risk evaluation to peer review in this manner, EPA will obtain the necessary independent review and advice for the 1,3-butadiene risk evaluation.

CHARGE QUESTIONS:

1. Environmental Exposure Assessment and Analysis

a) As described in the *Draft Environmental Release and Occupational Exposure Assessment for 1,3-Butadiene* (U.S. EPA, 2024d), 1,3-butadiene is primarily released to air. The vapor pressure, Henry's Law Coefficient, and partitioning coefficients of 1,3-butadiene indicate that the chemical does not partition to or persist in water or soil, and would be expected to volatilize quickly from water and land surfaces (*Draft Physical Chemistry and Fate Assessment for 1,3-Butadiene* (U.S. EPA, 2024e)). Monitoring data indicate that 1,3-butadiene is not detected in water (*Draft Environmental Media Concentrations for 1,3-Butadiene* (U.S. EPA, 2024a)). Physical and chemical properties of 1,3-butadiene indicate that the chemical does not partition, deposit, or persist in water or soil, and would be expected to volatilize quickly from water and land surfaces. Monitoring data indicate that 1,3-butadiene is not detected in water. EPA has concluded that contributions to exposure from the land and water pathways are expected to be small, and there is not expected to be exposure to aquatic and terrestrial species. Exposure of terrestrial organisms via ambient air is expected to be brief due to the reactive nature of 1,3-butadiene.

i) Please comment on EPA's conclusion to develop a qualitative assessment of 1,3-butadiene contributions to the land (groundwater, soil) and water (surface water, sediments, drinking water) (Section 6.1 of the *Draft Risk Evaluation for 1,3-Butadiene* (Section 6.1 of the *Draft Risk Evaluation for 1,3-Butadiene* (U.S. EPA, 2024f)).

ii) Please comment on EPA's conclusion to develop a qualitative assessment to ecological taxa (Section 6.2 of the *Draft Risk Evaluation for 1,3-Butadiene* (U.S. EPA, 2024f)).

2. General Population Exposure Assessment and Analysis

a) General population exposure to 1,3-butadiene by inhalation of 1,3-butadiene in ambient air was modeled using a tiered approach (*Draft General Population Exposures for 1,3-Butadiene* (U.S. EPA, 2024b). The concentrations of 1,3-butadiene in ambient air from facilities that use, manufacture, or process 1,3-butadiene under industrial and/or commercial COUs subject to TSCA were modeled with releases reported to the Toxic Release Inventory (TRI) for years 2016 to 2021 used as input. Screening-level modeling of ambient air concentrations was completed using the Integrated Indoor-Outdoor Air Calculator (IIOAC). Modeled results from IIOAC supported the need for refined modeling of ambient air concentrations to evaluate cancer risk. The Human Exposure Model (HEM) was used to model geographically refined ambient air concentrations, accounting for localized meteorological data and site-specific parameters (when available). HEM allows for estimation of ambient air concentrations at discrete distance rings

and at census block centroids surrounding each releasing facility. EPA acknowledges that NEI 2017 and 2020 data may provide refinement to exposure estimates and is evaluating data for inclusion in the final risk evaluation.

i) Please comment on EPA's approach and methodology with IIOAC modeling of ambient air concentrations to inform the non-cancer risk evaluation (Section 2.2.2 of the *Draft General Population Exposures for 1,3-Butadiene* (U.S. EPA, 2024b)).

ii) Please comment on EPA's approach and methodology with HEM modeling of ambient air concentrations (Section 2.2.3 of the *Draft General Population Exposures for 1,3-Butadiene* (U.S. EPA, 2024b)) based on both discrete distances and census blocks to inform the cancer risk evaluation (Sections 5.3.4.2 and 5.3.4.3 of the *Draft Risk Evaluation for 1,3-Butadiene* (U.S. EPA, 2024f)).

(1) Please comment on strengths and limitations of determining risk at radial distances.

(2) Please comment on strengths and limitations of determining risk at census blocks.

(3) Please comment on EPA's conclusion that refined modeling of ambient air concentrations was necessary to inform cancer risk evaluation.

iii) Please comment on the strengths and limitations of model inputs (*i.e.*, facility release information reported to TRI, such as stack height, fugitive area, days and hours of operation) (Sections 2.2.2, 2.2.3, 3.1 and 3.2 and Appendix B of the *Draft General Population Exposures for 1,3-Butadiene* (U.S. EPA, 2024b)).

iv) To characterize 1,3-butadiene concentrations in ambient air, both monitoring and modeling data were evaluated (Section 3.1.2 of the *Draft Environmental Media Concentrations for 1,3-Butadiene* (U.S. EPA, 2024a) and Section 2.3.1 of the *Draft General Population Exposures for 1,3-Butadiene* (U.S. EPA, 2024b)). Please comment on how both modeling and monitoring data can be used in a comprehensive evidence integration to inform characterization of ambient air concentrations.

3. Consumer Exposure Assessment

a) EPA has determined that 1,3-butadiene, a monomer used in polymer-derived consumer products such as synthetic rubbers, is stable in these products and not expected to degrade in such a way as to expose the consumer to the 1,3-butadiene monomer. These polymers include but are not limited to, acrylonitrile-butadiene-styrene (ABS) resins and styrene-butadiene rubber (SBR). Residual butadiene concentrations in polymers and downstream concentrations are very low and often not detectable.

i) Please comment on EPA's conclusion to develop a qualitative assessment of exposure to 1,3-butadiene in consumer products and articles (Sections 5.1.2 and 5.3.3 of the *Draft Risk Evaluation for 1,3-Butadiene* (U.S. EPA, 2024f)).

4. Occupational Exposure Assessment

a) EPA reviewed workplace inhalation monitoring data collected by government agencies such as OSHA and NIOSH, monitoring data found in published literature (*i.e.*, personal exposure monitoring data and area monitoring data), and monitoring data submitted by the American Chemistry Council (ACC) (docket ID: EPA-HQ-OPPT-2018-0451-0053). The data provided by ACC included 5,676 full-shift personal breathing zone (PBZ) samples for several classifications of workers and occupational non-users (ONUs) collected from member sites from a period of 2010 to 2019 ToxStrategies (2021). These data were found to be directly applicable to the manufacture, processing as a reactant, and incorporation into formulation COUs, and subsets of these data were used as analogous data for the repackaging, use of laboratory chemicals, disposal, and recycling COUs. Monitoring data from OSHA were used for the application of paints and coatings, application of adhesives and sealants, plastics and rubber compounding, and plastics and rubber converting COUs. Physical and chemical properties of 1,3-butadiene indicate that 1,3-butadiene is a gas at room temperature with a low tendency to partition to organic matter and liquid at below freezing temperatures (4.54 °C). Contact with liquid 1,3-butadiene will cause frostbite if proper gloves are not used thus dermal exposure to workers from contact with 1,3-butadiene is not expected. Therefore, the predominant pathway of exposure for occupational workers is expected to be inhalation.

i) Most occupational exposure monitoring data points – available from OSHA, NIOSH, and ACC's *Analysis of 1,3-Butadiene Industrial Hygiene Data* (docket ID: EPA-HQ-OPPT-2018-0451-0053) - were identified as being below the limit of detection (LOD) (see Table 3-3 and 3-4 of the *Draft Environmental Release and Occupational Exposure Assessment* (U.S. EPA, 2024d)).

As described in Section 2.4.3.1 of the *Draft Environmental Release and Occupational Exposure Assessment* (U.S. EPA, 2024d), for monitoring data that were reported as being below the LOD, EPA estimated exposure concentrations following EPA's Guidelines for Statistical Analysis of Occupational Exposure Data. Based on these guidelines, non-detects were scored as ½ the LOD value to allow for the values to be incorporated into summary statistics.

(1) Please comment on the ability of this approach to appropriately characterize exposures which may be below the LOD, while adequately accounting for the uncertainties inherent in measurements below the LOD.

(2) Please suggest alternative methods for quantitatively evaluating data sets with more than 50% of samples below LOD.

i) As described in Section 3.2.4.3, Section 3.8.4.3, Section 3.12.4.3, and Section 3.13.4.3 of the *Draft Environmental Release and Occupational Exposure Assessment for 1,3-Butadiene* (U.S. EPA, 2024d). Activity-specific monitoring data averaged across full-day work shifts and collected while completing specific tasks at manufacturing and processing facilities were available. However, monitoring data were not available for all occupational exposure scenarios (OESs) and COUs. When monitoring data were not available for a specific OES/COU, analogous data were used as described in Section 3.2.4.3, Section 3.8.4.3, Section 3.12.4.3, and Section 3.13.4.3 of the *Draft Environmental Release and Occupational Exposure Assessment for 1,3-Butadiene*.

ii) Analogous data are data from other OESs/COUs where activities and exposure profiles are expected to be similar.

(1) Please comment on the applicability of using activity-specific monitoring data as analogous data across OESs and COUs that perform similar occupational tasks.

(2) Please comment on EPA's conclusion to develop a qualitative assessment of dermal exposure to 1,3-butadiene for occupational workers based on 1,3-butadiene's physical and chemical properties.

5. Human Health Hazard

a) As described in Section 4.2.1.1 of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c), EPA did not identify any adverse effects associated with a single exposure at concentrations relevant to human exposure scenarios. Reduced fetal body weight (the basis of the acute reference concentration (RfC) in the 2002 IRIS Assessment) is observed in both mice and rats following gestational exposure but is not expected to result from a single dose of 1,3-butadiene. There are also no other effects on teratogenicity or other relevant endpoints observed following single exposures at doses relevant to human exposure scenarios. Therefore, EPA did not derive an acute point of departure (POD) or quantify risks from acute exposures.

i) Please comment on EPA's preliminary determination that there is no appropriate POD to support acute risk estimates.

b) EPA has proposed a mode of action associated with ovarian atrophy observed in mice (see Section 4.1.1.3 from the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c)). EPA proposed that there are species differences in the production of epoxide metabolites and evidence of greater toxicodynamic sensitivity in mice compared to rats. Humans are expected to be toxicokinetically less sensitive however toxicodynamic sensitivity is unknown. EPA has evaluated the relevance of ovarian atrophy for assessing human risk and determined that the ovarian atrophy endpoint is not appropriate for extrapolating to human risk due to differences in species-specific metabolites and inability to confidently determine any quantitative adjustment for humans.

i) Please comment on EPA's description of 1,3-butadiene toxicokinetics (see Section 3.3) and EPA's preliminary conclusion with regards to differences among mice, rats, and humans.

ii) Please comment on EPA's proposed mode of action for ovarian atrophy observed in mice (see Section 4.1.1.3).

iii) Please comment on EPA's preliminary conclusion that ovarian atrophy is not appropriate for extrapolating to human risk due to differences in species-specific metabolites and substantial uncertainty in quantifying the relevant metabolite concentrations in humans (see Section 4.1.1.3.7).

c) EPA has proposed to use decreased fetal body weight observed in mice as the basis for the intermediate and chronic points of departure for 1,3-butadiene (Section 4.2.2.3 of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c)). Developmental effects following gestational exposure were observed in both mice and rats, however mice were more sensitive.

The most sensitive point of departure (POD) from mice is used for risk estimates because it is protective of the other associated developmental outcomes and there is insufficient knowledge with respect to the available pharmacokinetic data in pregnant animals, fetuses, and early post-natal laboratory animals to indicate a role for any particular metabolite or differential toxicokinetic sensitivity across species. Relevant endpoints for dominant lethality and anemia were also benchmark dose (BMD) modeled but not used for risk characterization because fetal weight is the most sensitive and robust human-relevant endpoint.

i) Please comment on the strengths and limitations of decreased fetal body weight and associated gestational developmental toxicity as the critical endpoint.

ii) Please comment on the strengths and limitations of the approach to dichotomize the continuous fetal body weight data for BMD modeling, using methodology adapted from the 2002 IRIS assessment.

iii) Please comment on the selection of benchmark responses (BMRs) for all endpoints (*e.g.*, 5% for all developmental outcomes, and 1 standard deviation (SD) for maternal body weight and hematological measures).

iv) EPA recognizes that the BMDL for fetal body weight is below the lowest tested dose in the study. However, this analysis is robust and obviates the need to apply a LOAEL to NOAEL uncertainty factor that would be required by using the lowest dose as the POD. Please comment on EPA's discussion and consideration of modeling extrapolation relative to the tested concentrations (Section 4.2.2.2.1).

b) EPA conducted a mutagenic mode of action analysis (MMOA) and concluded that a mutagenic mode of action is applicable to the 1,3-butadine (Section 5.3 of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c)). Based on this preliminary determination, EPA used a linear dose-response approach with incorporation of age-dependent adjustment factors (ADAFs) in accordance with EPA guidance to derive the IUR for the general population.

i) Please comment on clarity, transparency and robustness of EPA's MMOA analysis and conclusions.

i) As described in Section 5.4.31 of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c). Please comment on the strengths and limitations of the selected model (restricted cubic spline, Cox regression) and parameters (lifetime, lag time, handling of peak exposure tasks, etc.) using the 95th exposure percentile and the corresponding β-coefficient (described in Table 5-7).

e) As described in Appendix C of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c), EPA derived an IUR for bladder cancer; however, EPA only had moderate confidence in this result because only two of the relevant seven publications identified a positive association, and they did not consider potential confounding from smoking in the selected model (Table_Apx C-1, exposed person-time, excluding unexposed model in Table_Apx C-2). For this reason, EPA did not combine bladder cancer with leukemia in deriving total cancer risk (IUR). EPA applied a lag time of 0 years in the modified lifetable analysis for bladder cancer for two reasons: (1) the model (Sathiakumar et al., 2021) that EPA chose to adopt the beta coefficient for lifetable analysis used the lag of 0 years and (2) the modeling of different lags time in exposure showed

little effect on beta coefficients, even though 20 years is considered as the minimum latency period after the start of exposure (Clin et al., 2014; Mazeman, 1972).

i) Please comment on the EPA's evidence integration and the weight of the scientific conclusions regarding bladder cancer.

ii) Please comment on the lag time for bladder cancer (0 years), which is used in the modified lifetable analysis.

iii) Please comment on the strengths and weakness of excluding bladder cancer from the total cancer risk (IUR) derivation.

f) As described in Section 5.4 of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c), the EPA revised the inhalation unit risk (IUR) for leukemia presented in the IRIS 2002 assessment to incorporate updated epidemiological occupational cohort data. A lifetable analysis was performed assuming exposure from 0 to 85 years of life and the ADAF was applied to the resulting unit risk for general population risk estimation. The risk evaluation for 1,3-butadiene currently reflects estimates based on the 0 to 85 lifetable IUR and UR. An error in the lifetable was detected in EPA's process of document finalization. An updated IUR for general population and UR for occupational exposure was derived and included as appendix F of the *Draft Human Health Hazard Assessment* (U.S. EPA, 2024c). The difference between the original and updated lifetables is childhood exposure; childhood exposure is now set to zero and the duration times adjusted accordingly.

i) Please comment on EPA's evaluation and incorporating new epidemiological cohort data in derivation of updated cancer hazard values, including study selection for dose-response analysis.

ii) Please comment on the strengths and limitations of the selected model (restricted cubic spline, Cox regression), which uses the 95th exposure percentile and the corresponding β-coefficient (described in Table 5-7).

iii) Please comment on the strengths and limitations of lifetable analysis, including variables and values, *e.g.*, lifetable age span (16 to 85 years), incidence, lag time = 0 years, etc.

iv) Please comment on the methodology for EPA's derivation of two distinct cancer unit risks – (a) the general population IUR incorporating ADAFs, and (b) the chronic occupational unit risk (UR) based on the same lifetable but without ADAFs.

v) Please comment on clarity, transparency, and robustness of EPA's MMOA analysis and conclusions.

6. Draft Risk Evaluation

a) It is important that the information presented in the risk evaluation and accompanying documents is clear and concise and describes the process in a scientifically credible manner. EPA's Risk Characterization Handbook cites transparency and clarity as two critical risk characterization principles. To this end, EPA is utilizing technical support documents to present information in a manner most appropriate for each component of the risk evaluation.

i) Please comment on the overall content, organization, and presentation of the technical support documents:

Draft Physical Chemistry and Fate Assessment for 1,3-Butadiene (U.S. EPA, 2024e)
Draft Environmental Media Concentrations for 1,3-Butadiene (U.S. EPA, 2024a)
Draft General Population Exposures for 1,3-Butadiene (U.S. EPA, 2024b)
Draft Environmental Release and Occupational Exposure Assessment (U.S. EPA, 2024d)
Draft Human Health Hazard Assessment (U.S. EPA, 2024c).

ii) Please provide suggestions for improving the clarity of the information presented and the technical information's usefulness for intended users and the public.

REFERENCES

Clin, B; Group, RW; Pairon, JC. (2014). Medical follow-up for workers exposed to bladder carcinogens: the French evidence-based and pragmatic statement [Review]. BMC Public Health 14: 1155. http://dx.doi.org/10.1186/1471-2458-14-1155

Mazeman, E. (1972). [Tumors of the upper excretory urinary tract, calices, renal pelvis and ureter]. J Urol Nephrol (Paris) 78.

Sathiakumar, N; Bolaji, B; Brill, I; Chen, L; Tipre, M; Leader, M; Arora, T; Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chem Biol Interact 347: 109600. http://dx.doi.org/10.1016/j.cbi.2021.109600

ToxStrategies. (2021). Analysis of 1,3-butadiene industrial hygiene data. Washington, DC: American Chemistry Council.

U.S. EPA (U.S. Environmental Protection Agency). (2024a). Draft Environmental Media Concentrations for 1,3-Butadiene. Washington, DC: Office of Pollution Prevention and Toxics.

U.S. EPA (U.S. Environmental Protection Agency). (2024b). Draft General Population Exposure for 1,3-Butadiene. Washington, DC: Office of Pollution Prevention and Toxics.

U.S. EPA (U.S. Environmental Protection Agency). (2024c). Draft Human Health Hazard Assessment for 1,3-Butadiene. Washington, DC: Office of Pollution Prevention and Toxics.

U.S. EPA (U.S. Environmental Protection Agency). (2024d). Draft Occupational Exposure Assessment for 1,3-Butadiene. Washington, DC: Office of Pollution Prevention and Toxics.

U.S. EPA (U.S. Environmental Protection Agency). (2024e). Draft Physical Chemistry and Fate Assessment for 1,3-Butadiene. Washington, DC: Office of Pollution Prevention and Toxics.

U.S. EPA (U.S. Environmental Protection Agency). (2024f). Draft Risk Evaluation for 1,3-Butadiene. Washington, DC: Office of Pollution Prevention and Toxics.