April 30, 2025

Dr. Anna Lowit
U.S. Environmental Protection Agency
Office of Chemical Safety and Pollution Prevention
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1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Ms. Alie Muneer
U.S. Environmental Protection Agency
OCSPP OPS Mission Support Division
Mail Code: 7201M
1200 Pennsylvania Ave., N.W.
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Re: TSCA Risk Evaluation of 1,3 Butadiene

Dear Dr. Lowit and Ms. Muneer,

The American Chemistry Council[1] (ACC) 1,3-Butadiene TSCA Risk Evaluation Consortium (Consortium) appreciates the opportunity to respond to the April 21, 2025, email request from Ms. Muneer's office to provide information regarding certain issues raised during the meeting of Science Advisory Committee on Chemicals (SACC) to review the TSCA risk evaluation of 1,3-Butadiene (1,3-BD). The Consortium strongly urges the EPA to continue its crucial work of maintaining and improving the integrity, transparency, and effectiveness of the TSCA Risk Evaluation process. Throughout the Agency's risk evaluation process, the Consortium has been committed to open communication and sharing of information. The Consortium has and will continue to be committed to providing the best available data to the Agency so that the final risk evaluation of 1,3-BD is based on the best available science. To this end, the Consortium sponsored studies that were conducted under the highest scientific standards and the Consortium stands by these studies.[2] In addition to all of the information that the Consortium has provided thus far, the Consortium hopes that the following information will assist EPA as it finalizes the risk evaluation.

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the multibillion-dollar business of chemistry. ACC members apply the science of chemistry to make innovative products, technologies and services that make people's lives better, healthier, and safer. ACC is committed to improved environmental, health, safety, and security performance through Responsible Care®; common sense advocacy addressing major public policy issues; and health and environmental research and product testing. ACC members and chemistry companies are among the largest investors in research and development, and are advancing products, processes, and technologies to address climate change, enhance air and water quality, and progress toward a more sustainable, circular economy.

[2] Human health risk assessment for exposures to 1,3-butadiene in the United States with input from an independent science advisory panel - PubMed

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The Consortium members are committed to responsible operations and to the safety and health of the communities in which they operate. Promoting the safe use of the essential products of chemistry is a shared responsibility of manufacturers, the government, and those who use or sell chemical products. Under TSCA, regulations must be based on the best available science and real-world exposure scenarios.

A. Confidence in the Exposure Estimates- The Macaluso et al. (2004) Study

We would like to address two issues regarding the SACC' s discussion of the exposure estimates for the styrene-butadiene rubber (SBR) cohort of Macaluso et al. (2004). First, members of the SACC were incorrect in referring to Macaluso et al. (2004) as relying upon modeled exposure estimates and that previous exposure assessments (i.e., prior to the 2004 paper) of the SBR cohort as relying upon industrial hygiene measurements. As noted in Macaluso et al. (1996), which served as the basis of the historical exposures to the SBR cohort used in EPA's 2002 assessment of 1,3-BD's cancer potency:

> *"The present investigation is the first in which mechanistic models have been used systematically to obtain exposure estimates for a large number of individual workers."*

Therefore, EPA's past estimates of 1,3-BD's cancer potency are also based upon modeled historical exposures to the SBR cohort.

Second, the SACC's discussion of SBR cohort exposure assessment was incomplete. For example, there are significant limitations of the available IH data for the SBR cohort, which were not mentioned by SACC members but were specifically discussed in Macaluso et al. (2004):

> *"Industrial hygiene (IH) data were not suitable for estimating exposure for several reasons. Plant data were limited, as IH monitoring programs began only in the late 1970s at most plants and were not necessarily designed to describe average workplace exposure levels. Some of the IH measurements were made to assess "worst case" exposure scenarios or to document problems, and overestimated average exposure levels. On the other hand, IH sampling done after the installation of new equipment or after scheduled maintenance may have underestimated average exposure conditions. Thus, it is difficult to interpret the published summaries of these data. Furthermore, whereas the design of the two NIOSH surveys was adequate, only a select group of work areas and jobs were evaluated, and the number of measurements taken for specific jobs was relatively small."*

In addition, there are two addition publications by the University of Alabama that increase confidence in the exposure estimates of Macaluso et al. (2004), namely an exposure validation study (Sathiakumar et al., 2006) and an exposure uncertainty analysis (Graff et al., 2009).

In the validation study, Sathiakumar et al. (2006) compared the modeled estimates of exposure to 4978 measurements initiated in 1977. On average, the modeled estimates were slightly lower (~10%) than the measured values, which indicates that the application of the modeled data in estimating cancer potency

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serves to underestimate potency by the same margin on average. For risk assessment purposes, a 10% difference is considered to be a relatively small source of uncertainty.

In the uncertainty assessment, Graff et al. (2009) created 1000 sets of 1,3-BD exposure estimates using job-exposure matrices consisting of exposure values that corresponded to randomly selected percentiles of the approximate probability distribution of plant-, work area/job group-, and year-specific 1,3-BD concentrations. The authors then examined the impact of this uncertainty on resulting relative rates for leukemia. For the relative rate of leukemia, the minimum and maximum values determined based upon uncertainty in the exposure estimates were within 20% of the mean relative rate for the first quartile (considered as a surrogate for a corresponding point of departure value for leukemia). For risk assessment purposes, a 20% difference is considered to be a relatively small source of uncertainty.

In addition, Macaluso et al. (2004) summarizes the limitations of the industrial hygiene data for 1,3-BD: "Industrial hygiene (IH) data were not suitable for estimating exposure for several reasons." Plant data was limited, as IH monitoring programs began only in the late 1970s at most plants and were not necessarily designed to describe average workplace exposure levels. Some of the IH measurements were made to assess "worst case" exposure scenarios or to document problems and overestimated average exposure levels. On the other hand, IH sampling done after the installation of new equipment or after scheduled maintenance may have underestimated average exposure conditions. Thus, it is difficult to interpret the published summaries of these data. Furthermore, whereas the design of the two NIOSH surveys was adequate, only a select group of work areas and jobs were evaluated, and the number of measurements taken for specific jobs was relatively small.

B. Consideration of Sensitive Subpopulations

Existing risk assessments address sensitive subpopulations due to elevated CYP2E1 activity (e.g., due to alcohol consumption, obesity). For example, the SBR cohort is sufficiently large (n=22,785; Sathiakumar et al., 2021a,b) such that these factors are well represented by the population of workers used to estimate the cancer potency. In addition, the use of hemoglobin adduct data to account for species differences in the toxicokinetics of BD (Kirman et al., 2022) relies upon a population of workers from the Czech Republic, which while smaller than the SBR cohort (n>150) is still expected to provide adequate coverage for these factors, particularly since the Czech Republic has (now and historically) one of the highest per capita alcohol consumptions in Europe according to the WHO's annual European Health Report (https://www.who.int/europe/publications/i/item/WHO-EURO-2025-10668-50440-76183).

The absence of a trend in the hemoglobin adduct data for 1,3-BD's diepoxide metabolite (pyr-val) in female Czech Republic workers may be attributed to a number of factors including: (1) contributions from and variation in exposure pathways outside the workplace (e.g., pyr-Val biomarker levels in exposed female workers are not elevated over background levels) ; (2) exposure variation and uncertainty (e.g., air sampling not capturing high-exposure events during the sampling window); (3) analytical variation; and (4) potentially higher variation in BD metabolism in women compared to men. Regardless of the presence or absence of a trend, the primary conclusion of these data is that they are approximately three

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orders of magnitude lower than that measured in exposed mice, and therefore the observation by SACC members does not impact the use of these data for interspecies extrapolation.

C. Consideration of Combined Leukemia and Bladder Cancer Risks

SACC members discussed the inclusion of other cancer types (e.g., bladder cancer, breast cancer) in the quantitative assessment. However, their discussion did not appear to include two important considerations. First, the members did not appear to recognize that a causal relationship between BD exposure and cancers other than leukemia has not been established, and therefore their inclusion in quantitative estimates of cancer potency is not warranted or supported. Second, the SACC's discussion did not recognize that as part of a sensitivity analysis (i.e., what if a causal relationship was assumed now or established in the future?), Valdez-Flores et al. (2022) specifically considered the inclusion of potential bladder cancer risks in an aggregate risk endpoint (leukemia and/or bladder cancer). As shown in Table 11 of this paper, the impact of including bladder cancer risk in the quantitative potency estimate is relatively small (i.e., less than a factor of 2), resulting in an approximate 7% change in the Cox regression slope (0.00002808 vs. 0.0002991) and an approximately 34% change in the lower confidence limit for the point of departure (0.0085 vs 0.0056 ppm), which reflects the impact of including bladder cancer in the life-table calculations in addition to the change in the slope value.

D. Flaring Operations

The Consortium agrees that flaring events are outside the scope of the TSCA risk evaluation. These events are covered by other Federal and State environmental agencies, such as the Texas Commission on Environmental Quality (TCEQ) and the Louisiana Department of Environmental Quality (LDEQ). Nevertheless, it is important to acknowledge that major manufacturing facilities producing 1,3-BD operate continuously, and controlled flaring of hydrocarbons is a necessary and well-established safety measure integral to maintaining safe plant operations.

* *

The Consortium appreciates EPA's consideration of this information as well as comments previously submitted to the OPPT and the SACC Dockets (Docket ID EPA-HQ-OPPT-2018-0451, Docket ID EPA-HQ-OPPT-2024-0425), and via the CDX platform. The Consortium is available to meet with EPA to provide additional clarity and context on technical issues in the letter and other questions that may arise as the Agency finalizes the 1,3-BD draft risk evaluation. If you have any questions, please contact me at (202) 249-6712 or at Neeraja_erraguntla@americanchemistry.com.

Sincerely,

Neeraja Erraguntla

Director, Chemical Products and Technology

cc: Brooke Porter, Sheila Healey, Kathy Dionisio, Tamue Gibson

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