OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

November 25, 2024

MEMORANDUM

SUBJECT: 1,3-Butadiene: Corrected lifetable analyses for leukemia and bladder cancer

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TO: Jeff Morris, Director
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PURPOSE: This memo corrects an error in OPPT's draft lifetable and cancer risk of 1,3-butadiene provided in the *Draft Lifetable Analysis of Leukemia and Bladder Cancer* supplemental file (U.S. EPA, 2024a) and used in the *Draft Risk Evaluation for 1,3-Butadiene* (U.S. EPA, 2024b).

REVISED ANALYSIS: EPA has determined that 1,3-Butadiene is "Carcinogenic to Humans" and exhibits a mutagenic mode of action as described in the *Draft Human Health Hazard Assessment for 1,3-Butadiene* (U.S. EPA, 2024c). Epidemiological studies in the US-Canadian styrene-butadiene rubber (SBR) worker cohort are available for deriving cancer risk values. In the *Draft Human Health Hazard Assessment for 1,3-Butadiene* (U.S. EPA, 2024c), a general population inhalation unit risk (IUR) and chronic occupational unit risk (UR) for leukemia and bladder cancer were derived based on lifetime exposure (0–78 years). A miscalculation error was identified in applying the age-dependent adjustment factor (ADAF) in the late stage of EPA internal review and clearance. Accordingly, the lifetable was revised to initiate exposure to 1,3-butadiene at 16 years of age —instead of at birth (as was done in the initial IUR). Sixteen is assumed to be the age at which occupational exposure begins (U.S. Department of Labor, 2016) and is also the age when an ADAF is no longer applied. This revised lifetable estimates the unit risks for the 62-year period between age 16 years and age 78 years (OPPT's assumption of a lifetime). This unit risk is also the chronic occupational UR. For the general population IUR, the

occupational UR estimates were then multiplied by 78 ÷ 62 to rescale the 62-year adult period to 78 years (U.S. EPA, 2024e). Finally, in accordance with the EPA 2005 *Supplemental Guidance for Assessing Susceptibility from Early-life Exposure to Carcinogens*, the following ADAFs were applied to the adult unit risk: 10 for children ages less than 2 years; 3 for children ages 2 to 15; and 1 for persons aged 16 to 78. The weighted sum of these three partial unit risks is the ADAF-adjusted lifetime IUR. EPA is soliciting peer review from the SACC on the derivation of the UR and IUR in February 2025.

CONCLUSION:

The leukemia IUR that is used to estimate general population risk has not changed meaningfully; after rounding, the general population IUR values are nearly the same (Table 5-8, appended and Table_Apx F-1. Modified Table 5-8 below in this memo). Therefore, overall risk conclusions for the general population (Section 4.3.7.2 in the *Draft Risk Evaluation for 1,3-Butadiene*) remain the same.

For the occupational leukemia UR, correcting the lifetable to initiate exposure at age 16 reduces the chronic occupational leukemia UR from 0.0062 per ppm (Table 5-8, appended) to 0.0049 per ppm (Table_Apx F-1. Modified Table 5-8 below in this memo). Reduction (~ ↓20%) of the chronic occupational leukemia UR is not expected to change risk conclusions at the central tendency in Table 5-4 of the *Draft Risk Evaluation for 1,3-Butadiene* (*i.e.,* no central tendency risk estimates cross the benchmark threshold of 1×10^{-4} as a result of this change). These lifetable corrections will be incorporated after peer review of the *Draft Risk Evaluation for 1,3-Butadiene* and prior to release of the *Risk Evaluation for 1,3-Butadiene.* The occupational risk estimate in the *Draft Risk Evaluation for 1,3-Butadiene* will also be updated accordingly after peer review and before release of the *Risk Evaluation for 1,3-Butadiene*.

CORRECTION: The lifetable analyses were revised to initiate exposure at age 16 in the supplemental file *Modified Lifetable Analysis of Leukemia and Bladder Cancer for 1,3-Butadiene* (U.S. EPA, 2024d) and yielded the estimates in modified tables Table_Apx F-1. Modified Table 5-8, Table_Apx F-2. Modified Table 8-3, Table_Apx F-4. Modified Table_Apx C-3 and Table_Apx F-5. Modified Table_Apx C-4 below. These modified tables are appended in Appendix F of the *Draft Human Health Hazard Assessment for 1,3-Butadiene* (U.S. EPA, 2024c).

Table_Apx F-1. Modified Table 5-8 Calculation of Leukemia Unit Risk Estimate

Model of the Beta-Coefficient (β), Reference	β		Exposure Concentration Associated with BMR (1% Extra Risk) Starting Exposure at Age 16 Year		Adult-exposure-only Unit Risk (62 year)[d]		Adult-based Unit Risk (78 year)[e]	
	MLE[a]	95% UB[b]	EC_{01} (16+) MLE	LEC_{01} (16+) 5% LB[c]	MLE	95% UB[b]	MLE	95% UB[b]
Cox regression model Sathiakumar et al. (2021b)	0.00094	0.0018	3.89 ppm	2.04 ppm	0.0026 per ppm	0.0049 per ppm	0.0032 per ppm	0.0062 per ppm

[a] MLE means Maximum Likelihood Estimate, a statistical method for estimating a population parameter most likely to have produced the sample observations.

[b] UB means the upper bound estimate.

[c] LB means the lower bound estimate.

[d] Adult-exposure-only Unit Risk (62 year) means the unit risks for the 62-year period between age 16 years and age 85 years (OPPT assumption of a lifetime).

[e] Adult-based Unit Risk (78 year) means to rescale the 'adult-exposure-only' unit risk from 62-year adult period to 78-years by multiplying by 78 ÷ 62.

Table_Apx F-2. Modified Table 8-3 Incorporation of Age-Dependent Adjustment Factors for General Population Risk Estimation for Leukemia

Age	ADAF Adjustment[a]	General Population IUR Computation
0 to <2	10×	0.0062 × 10 × (2/78) = 0.0016
2 to <16	3×	0.0062 × 3 × (14/78) = 0.0033
≥16[b]	1×	0.0062 × 1 × (62/78) = 0.0049
0 to 78		**0.0098 per ppm (4.4E−06 per µg/m^3)**

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

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

Table_Apx F-4. Modified Table_Apx C-3 Calculation of bladder cancer unit risk estimate

Model of the Beta-Coefficient (β), Reference	β		Exposure Concentration Associated with BMR (1% Extra Risk) Starting Exposure at Age 16 Year		Adult-exposure-only Unit Risk (62 year)[d]		Adult-based Unit Risk (78 year)[e]	
	MLE[a]	95% UB[b]	EC_{01} (16+) MLE	LEC_{01} (16+) 5% LB[c]	MLE	95% UB[b]	MLE	95% UB[b]
Cox regression model Sathiakumar et al. (2021a)	0.00035	0.000556	7.08 ppm	4.46 ppm	0.0014 per ppm	0.0022 per ppm	0.0018 per ppm	0.0028 per ppm

[a] MLE means Maximum Likelihood Estimate, a statistical method for estimating a population parameter most likely to have produced the sample observations

[b] UB means the upper bound estimate.

[c] LB means the lower bound estimate.

[d] Adult-exposure-only Unit Risk (62 year) means the unit risks for the 62-year period between age 16 years and age 85 years (OPPT assumption of a lifetime).

[e] Adult-based Unit Risk (78 year) means to rescale the 'adult-exposure-only' unit risk from 62-year adult period to 78-years by multiplying 78 ÷ 62.

Table_Apx F-5. Modified Table_Apx C-4 Incorporation of Age-Dependent Adjustment Factors for General Population Risk Estimation for Bladder Cancer

Age	ADAF Adjustment[a]	General Population IUR Computation
0 to <2	10×	0.0028 × 10 × (2/78) = 0.00072
2 to <16	3×	0.0028 × 3 × (14/78) = 0.0015
≥16[b]	1×	0.0028× 1 × (62/78) = 0.0022
0 to 78		**0.0045 per ppm (2.03E−06 per µg/m^3)**

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

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

TECHNICAL SUPPORT DOCUMENTS

The below listed technical support documents referenced within this memorandum are available on the docket. Files are numbered corresponding with the filenames uploaded to the docket: https://www.regulations.gov/docket/EPA-HQ-OPPT-2024-0425

7. *Draft Human Health Hazard Assessment for 1,3-Butadiene* (U.S. EPA, 2024c)

29. *Draft Lifetable Analysis of Leukemia and Bladder Cancer for 1,3-Butadiene* (U.S. EPA, 2024a)

30. *Modified Lifetable Analysis of Leukemia and Bladder Cancer for 1,3-Butadiene* (U.S. EPA, 2024d)

REFERENCES

Sathiakumar, N; Bolaji, B; Brill, I; Chen, L; Tipre, M; Leader, M; Arora, T; Delzell, E. (2021a). 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

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

U.S. EPA. (2005). Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. https://www.epa.gov/risk/supplemental-guidance-assessing-susceptibility-early-life-exposure-carcinogens.

U.S. EPA. (2011). Exposure factors handbook. https://www.epa.gov/expobox/exposure-factors-handbook-2011-edition.

U.S. Department of Labor. (2016). Fact Sheet #43: Child Labor Provisions of the Fair Labor Standards Act (FLSA) for Nonagricultural Occupations. https://www.dol.gov/agencies/whd/fact-sheets/43-child-labor-non-agriculture.

U.S. EPA. (2024a). Draft Lifetable Analysis of Leukemia and Bladder Cancer. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/11799950.

U.S. EPA. (2024b). Draft Risk Evaluation for 1,3-Butadiene. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/11363699.

U.S. EPA. (2024c). Draft Human Health Hazard Assessment for 1,3-Butadiene. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/11799949 .

U.S. EPA. (2024d). Modified Lifetable Analysis of Leukemia and Bladder Cancer. https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/12070935.

U.S. EPA. (2024e). IRIS Toxicological Review of Hexavalent Chromium [Cr(VI)] CASRN 18540-29-9 https://iris.epa.gov/static/pdfs/0144tr.pdf.

APPENDIX: Initial Draft Tables (Contain Miscalculation)

ERRATA: The following tables from the *Draft Human Health Hazard Assessment for 1,3-Butadiene* (U.S. EPA, 2024c) are based on the lifetable analyses which include exposure from year 0 and are found in the supplemental file *Draft Lifetable Analysis of Leukemia and Bladder Cancer for 1,3-Butadiene* (U.S. EPA, 2024d).

Table 5-8. Calculation of Leukemia Unit Risk Estimate

Model of the Beta-Coefficient (β), Reference	β		Exposure Concentration Associated with BMR (1% Extra Risk) Starting Exposure at Age <1 Years (µg/m^3)		Unit Risk	
	MLE[a]	95% UB[b]	EC_{01} MLE	LEC_{01} 5% LB[c]	MLE	95% UB[b]
Cox regression model Sathiakumar et al. (2021b)	9.94E−04	0.0018	2.9 ppm	1.62 ppm	0.0034 per ppm	**0.0062 per ppm**

[a] MLE means Maximum Likelihood Estimate, a statistical method for estimating a population parameter most likely to have produced the sample observations. This will be used for potential benefits analysis.
[b] UB means the upper bound estimate. This is the IUR to be used for risk estimation.
[c] LB means the lower bound estimate.

Table 8-3. Incorporation of Age-Dependent Adjustment Factors for General Population Risk Estimation

Age	ADAF Adjustment[a]	Adjusted Partial Life 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[b]	1×	0.0062 × 1 × (62/78) = 0.0049
0 to 78	**1.59**	**0.0098 per ppm (4.4E−06 per µg/m^3)**

[a] ADAFs are applied based on the determination of a mutagenic MOA (Section 5.3) and in accordance with (U.S. EPA, 2005).
[b] Adjusted IUR value is based on an assumption of 78 years lifetime (U.S. EPA, 2011).

Table_Apx C-3. Calculation of Bladder Cancer Unit Risk Estimate

Model of the Beta-Coefficient (β), Reference	β		Exposure Concentration Associated with BMR (1% Extra Risk) Starting Exposure at Age <1 years (µg/m^3)		Unit Risk	
	MLE[a]	95% UB[b]	EC_{01} MLE	LEC_{01} 5% LB[c]	MLE	95% UB[b]
Cox regression model Sathiakumar et al. (2021a)	3.50E−04	5.56E−04	7.90 ppm	5.0 ppm	0.0013 per ppm	0.002 per ppm

[a] MLE means Maximum Likelihood Estimate, a statistical method for estimating a population parameter most likely to have produced the sample observations.
[b] UB means the upper bound estimate.
[c] LB means the lower bound estimate

Table_Apx C-4. Incorporation of Age-Dependent Adjustment Factors for General Population Risk Estimation

Age	ADAF Adjustment[a]	Adjusted Partial Life and General Population IUR
0 to <2	10×	0.002 × 10 × (2/78) = 0.00051
2 to <16	3×	0.002 × 3 × (14/78) = 0.0011
≥16[b]	1×	0.002 × 1 × (62/78) = 0.0016
0 to 78		**0.0032 per ppm (1.4E−6 per µg/m^3)**

[a] ADAFs are applied based on the determination of a mutagenic MOA (Section 5.3) and in accordance with (U.S. EPA, 2005).
[b] Adjusted IUR value is based on an assumption of 78 years lifetime (U.S. EPA, 2011).