September 23rd, 2024

Comments from University of California, San Francisco Program on Reproductive Health and the Environment on the 1-Bromopropane (1-BP) Proposed Rule under the Toxic Substances Control Act (TSCA)

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2020-0471

These comments are submitted on behalf of the University of California, San Francisco Program on Reproductive Health and the Environment. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. Institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support, unless indicated otherwise.

We appreciate the opportunity to provide written comments on EPA's proposed rule for 1-bromopropane (1-BP) (hereafter referred to as the *1-BP Proposed Risk Management Rule*)[1] issued under the Toxic Substances Control Act ("TSCA"), which requires EPA to evaluate chemical risks based on the "best available science."[2] 1-BP is associated with serious health harms, and millions of pounds of 1-BP are manufactured in the US each year. 1-BP is primarily used as an industrial and commercial solvent in applications like cleaning and degreasing, dry cleaning, and as insulation for building materials. 1-BP is also used in consumer products, including spot cleaners, stain removers, and arts and crafts materials. EPA has identified both cancer and non-cancer health hazards of 1-BP exposure, including skin and lung cancers, as well as adverse renal, liver, nervous system, and reproductive effects.[3]

In the 1-BP Proposed Risk Management Rule, EPA continued to rely on the flawed "Margin of Exposure" (MOE) approach to non-cancer risk quantification that violates TSCA's "best available science" requirement. While EPA found that liver, kidney, developmental, reproductive and neurological toxicity are likely hazards of 1-BP, it failed to provide quantitative estimates of those non-cancer risks. We applied methods developed by the World Health Organization ("WHO") to quantify the non-cancer risk of developmental and neurological harm from chronic 1-BP inhalation exposure, and found that exposures that EPA previously determined result in "negligible concerns for adverse human health effects" produced an upper bound risk of 1-in-100 for developmental harm and 1-in-333 for neurological harm, risk levels *10,000 and 3,000 times higher,* respectively, than the target risk level that EPA typically applies for protection of carcinogenic risks (1-in-1,000,000). Exposure at EPA's proposed existing chemical exposure limit ("ECEL") produces a 1-in-1,000 risk level for developmental harm, and a greater than 1-in-10,000 risk level for neurological harm.[4] These risks also far exceed EPA's usual target risk level for carcinogenic risks of 1-in-1,000,000.

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[1] 1-Bromopropane (1–BP); Regulation Under the Toxic Substances Control Act (TSCA). Proposed Rule. 89 FR 65066, August 8, 2024.
[2] 15 U.S.C. § 2625(h).
[3] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide).
[4] 1-Bromopropane (1–BP); Regulation Under the Toxic Substances Control Act (TSCA). Proposed Rule. 89 FR 65066, August 8, 2024.

Accordingly, EPA must make extensive revisions to the 1-BP Proposed Risk Management Rule to more accurately characterize real-world risks, including adopting best available scientific methods that more accurately quantify non-cancer risks.

Our detailed comments on the 1-BP Proposed Risk Management Rule address the following issues:

1. **EPA failed to apply best available methods to generate quantitative risk estimates for varying levels of exposure to 1-BP for multiple liver, kidney, developmental, reproductive and neurological endpoints.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

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1. **EPA should apply best available methods to generate quantitative risk estimates for varying levels of exposure to 1-BP for multiple liver, kidney, developmental, reproductive and neurological endpoints.**

The 1-BP Proposed Risk Management Rule continues to rely on scientifically-deficient methods for non-cancer dose-response analysis and risk characterization employed in previous TSCA risk evaluations and proposed risk management rules. EPA's methods for non-cancer risk evaluation do not provide a quantitative estimate of risk. Instead, they rely on calculation of a margin of exposure ("MOE"), defined as:

> Margin of Exposure = Non-cancer point of departure / Human exposure.[5]

The MOE approach is a scientifically inappropriate approach for characterizing risk and is inconsistent with TSCA's requirements to use the "best available science"[6] and to ensure protection of "potentially exposed and susceptible subpopulations" ("PESS").[7]

Use of the MOE, which relies on a point of departure ("POD") with no extrapolation to lower doses, is a simplistic approach that only examines the ratio of the POD to the exposure level and determines whether this ratio is "interpreted as a potential human health concern" or if it "indicated negligible concerns for adverse human health effects."[8] The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected, and it perpetuates the scientifically flawed notion that a "safe" or "no risk" level of chemical exposure can be identified for a diverse exposed population.[9,10] The National Academies[11] and the World Health Organization ("WHO")[12,13] have outlined more robust methods for risk estimation that more accurately account for variability and

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[5] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 242.
[6] 15 U.S.C §2625 (h).
[7] 15 U.S.C §2602 (12).
[8] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 243.
[9] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., ...Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: overview and consensus statement. Environ Health, 21(Suppl 1), 132. https://doi.org/10.1186/s12940-022-00930-3.
[10] McGartland, A., Revesz, R., Axelrad, D. A., Dockins, C., Sutton, P., Woodruff, T. J. (2017). Estimating the health benefits of environmental regulations. Science, 357(6350), 457-458. https://doi.org/10.1126/science.aam8204.
[11] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Chapter 5.
[12] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.
[13] Chiu WA, Slob W. A Unified Probabilistic Framework for Dose–Response Assessment of Human Health Effects. Environmental Health Perspectives, 2015 December;123(12): 1241–1254. doi:10.1289/ehp.1409385.

vulnerability across the human population and have been demonstrated in published case studies.[14,15,16,17]

We applied the WHO methodology to estimate risks of adverse effects from chronic inhalation exposure to 1-BP using EPA's identification of hazards and estimation of points of departure (PODs). Specifically, we estimated risks of decreased brain weight (a developmental effect), and decreased traction time (a neurological effect that is an indicator of reduced muscle strength). We found that:

- 0.17 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 1% of the exposed population, and 0.29 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 1% of the exposed population.
- 0.06 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 0.1% of the exposed population, and 0.10 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 0.1% of the exposed population.
- 0.03 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 0.01% (1-in-10,000) of the exposed population, and 0.04 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 0.01% (1-in-10,000) of the exposed population.
- 0.01 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 0.001% (1-in-100,000) of the exposed population, and 0.02 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 0.001% (1-in-100,000) of the exposed population.

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk in the *Risk Evaluation for 1-Bromopropane* and comparison with EPA's proposed workplace exposure limits. The lowest non-cancer POD in EPA's risk evaluation is 17 ppm and has a benchmark MOE of 100,[18] meaning that EPA concludes for non-cancer outcomes that there are "negligible concerns for adverse human health

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[14] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z.

[15] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368.

[16] Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environment International, 2020 October;143:105953. doi: 10.1016/j.envint.2020.105953.

[17] Ginsberg, G. L. (2012). Cadmium risk assessment in relation to background risk of chronic kidney disease. J Toxicol Environ Health A, 75(7),374-390. https://doi.org/10.1080/15287394.2012.670895.

[18] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), Table 3-2.

effects"[19] for any 1-BP exposure below 0.17 ppm (17 ppm / 100 = 0.17 ppm). Our analysis indicates that an exposure of 0.17 ppm is equal to the lower-bound dose for the 1% (1-in-100) risk level for decreased brain weight, and is equal to the lower-bound dose for the 0.3% (1-in-333) risk level for decreased traction time. These risks far exceed EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[20]

EPA has proposed an existing chemical exposure limit ("ECEL") of 0.05 ppm, which it says "represents the concentration at which an adult human, including a member of a PESS, would be unlikely to suffer adverse effects if exposed for a working lifetime" and "will eliminate any unreasonable risk of injury to health from occupational inhalation exposures."[21] Our analysis indicates that an exposure of 0.05 ppm is just below the lower-bound dose for the 0.1% (1-in-1,000) risk level for decreased brain weight, and is greater than the lower-bound dose for the 0.01% (1-in-10,000) risk level for decreased traction time. These risks also exceed EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[22]

To better inform the final rule, EPA should apply the WHO framework to estimate risks of a range of kidney, liver and reproductive endpoints, as well as additional developmental and neurological endpoints. EPA's final rule should target any upper bound risks of noncancer effects from 1-BP exposure to be no more than the 1-in-1,000,000 risk level.

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[19] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 243.
[20] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 320.
[21] 1-Bromopropane (1–BP); Regulation Under the Toxic Substances Control Act (TSCA). Proposed Rule. 89 FR 65066, August 8, 2024.
[22] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 320.

Technical Appendix: Application of IPCS framework to 1-BP non-cancer risks

In the *Risk Evaluation for 1-Bromopropane*, EPA identified multiple hazards of 1-bromopropane (1-BP), including liver, kidney, reproductive, developmental and neurological effects. For risk characterization of these non-cancer health effects, EPA calculated a "margin of exposure" (MOE) for each condition of use, which is the ratio of the point of departure (POD) to the exposure level. For most effects of 1-BP, the risk evaluation concluded that a "benchmark MOE" of 100 or greater "indicated negligible concerns for adverse human health effects."[23]

EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population, but instead simply applies a "bright line" judgment of whether or not the MOE is adequate. A more informative approach for both risk characterization and risk management would be to apply the probabilistic dose-response assessment methods of the International Programme on Chemical Safety (IPCS),[24] part of the World Health Organization (WHO), to estimate the risk of adverse effects at various levels of exposure. The IPCS methodology has previously been described and applied in several peer-reviewed journal articles.[25,26,27,28,29]

We applied the IPCS approach for "quantal-deterministic" and continuous endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[30] to estimate risks of two selected 1-BP endpoints: decreased brain weight (a developmental effect), and decreased traction time (a neurological effect that is an indicator of reduced muscle strength). The IPCS framework is equally applicable to any endpoint identified by EPA in Table 3-2 of the 1-BP risk evaluation, and EPA should upgrade its evaluation of 1-BP risks using the IPCS methodology to better inform its final risk management rule by estimating risks of a range of kidney, liver and reproductive endpoints, as well as additional developmental and neurological endpoints.

The analysis of decreased brain weight and decreased traction time for 1-BP involved the following steps:

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[23] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 243.
[24] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.
[25] Chiu WA, Slob W. A Unified Probabilistic Framework for Dose–Response Assessment of Human Health Effects. Environmental Health Perspectives, 2015 December;123(12): 1241–1254. doi:10.1289/ehp.1409385.
[26] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z.
[27] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368.
[28] Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environment International, 2020 October;143:105953. doi: 10.1016/j.envint.2020.105953.
[29] Chiu WA, Paoli GM. Recent Advances in Probabilistic Dose–Response Assessment to Inform Risk-Based Decision Making. Risk Analysis, 2021 April;41(4):596-609. doi: 10.1111/risa.13595.
[30] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

1. Derivation of IPCS POD and corresponding uncertainty adjustments
2. Application of interspecies adjustments
3. Application of intraspecies adjustments
4. Calculation of HD_M^I - the human dose (HD) of 1-BP associated with a particular magnitude of effect M at a particular population incidence I.

For each aspect of the analysis, including the values used to derive the IPCS POD and the adjustment factors applied to derive the HD_M^I, the IPCS methodology uses a 50th percentile value (P50) as a central estimate and the ratio of 95th percentile to 50th percentile (P95/P50) as a measure of uncertainty. For each endpoint, we derive a set of inhalation HD_M^I values for different levels of population incidence (e.g. 1%, 0.1%, etc.). All POD and HD_M^I values presented in this analysis are for 8-hour time-weighted averages (8-hr TWA).

STEP 1: Derivation of IPCS POD and corresponding uncertainty adjustments

The IPCS methodology classifies each toxicity endpoint into one of three categories: continuous endpoints, quantal-deterministic endpoints, and quantal-stochastic endpoints. Procedures for determining the IPCS POD differ across these categories, and also differ depending on whether the POD provided by EPA is a benchmark dose (BMD), no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL). Because of these differences, we present the derivation of the IPCS POD separately for each of the two endpoints analyzed.

a. IPCS POD for decreased brain weight

EPA's risk evaluation for 1-BP states that there was no adequate fit to the data for any BMD model for decreased brain weight in adult F1 males,[31] and presents a duration-adjusted LOAEL of 110 ppm as the POD.[32]

Decreased brain weight is considered a quantal-deterministic endpoint in the IPCS framework. The IPCS methodology requires the use of an ED_{50} (median effective dose) value as the POD for quantal-deterministic endpoints. Since an ED_{50} is not available from the EPA risk evaluation, we applied adjustments provided by the IPCS methodology to derive an ED_{50} from a LOAEL. The first adjustment applies a factor to convert the LOAEL to a NOAEL. For this adjustment, Chiu et al. 2018 recommends applying as a central estimate (P50) the traditional LOAEL-to-NOAEL uncertainty factor reported in the existing EPA assessment, which in this instance was a factor of 10, and a P95/P50 ratio representing uncertainty equal to 3.[33]

[31] U.S. EPA (2020). Final Risk Evaluation for1-Bromopropane (*n*-Propyl Bromide), Supplemental Information on Human Health Benchmark Dose Modeling, p. 94.
[32] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), Table 3-2.
[33] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368.

The second adjustment is to then apply a factor to convert the NOAEL to an ED_{50}. For quantal-deterministic endpoints, the IPCS recommends a central estimate (P50) of 2/9 and a P95/P50 ratio representing uncertainty equal to 5.[34]

The median (P50) estimate of the ED_{50} is then derived by dividing the LOAEL by the two adjustment factors (P50). The uncertainty adjustments (P95/P50) for each POD aspect are combined into a composite P95/P50 value. In the IPCS approximate probabilistic calculation template, those values are entered as follows:

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic 1-BP inhalation: Decreased brain weight in adult F1 males		
Aspect	**P50**	**P95/P50**
LOAEL	110 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$[b]	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$[c]	0.22	5
IPCS POD = ED_{50}	**49.5 ppm**	**7.02[d]**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50).
[b] The EPA risk evaluation applied a LOAEL-to-NOAEL adjustment factor of 10 for this endpoint.
[c] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1.
[d] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 3)^2 + (\log 5)^2]^{0.5}} = 7.02$

b. IPCS POD for decreased traction time

For decreased traction time, a continuous endpoint, EPA conducted BMD modeling and derived a benchmark concentration (BMC) of 37 ppm and lower confidence limit on the BMC (BMCL) of 18 ppm.[35] EPA applied a duration adjustment to the BMCL to estimate a POD of 25 ppm.[36]

For continuous endpoints, the IPCS framework uses the BMC as the P50 value. We applied the outcome of EPA's duration adjustment to the BMC to arrive at a duration-adjusted BMC:

$$BMC_{adj} = BMC \times (BMCL_{adj} / BMCL) = 37 \text{ ppm} \times (25 \text{ ppm} / 18 \text{ ppm}) = 51 \text{ ppm}$$

[34] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1.
[35] U.S. EPA (2020). Final Risk Evaluation for1-Bromopropane (*n*-Propyl Bromide), Supplemental Information on Human Health Benchmark Dose Modeling, Table 2-91.
[36] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), Table 3-2.

Uncertainty in the BMC is represented by the ratio of 95th percentile to 50th percentile (P95/P50), which is equal to the ratio of BMC / BMCL. In this case, P95/P50 = BMC / BMCL = 37 ppm / 18 ppm = 2.06.

These values are entered in the IPCS approximate probabilistic calculation template as follows:

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic 1-BP inhalation: Decreased traction time		
Aspect	**P50**	**P95/P50**
IPCS POD = BMC[b]	**51 ppm**	**2.06**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50).
[b] EPA duration adjustment applied to reported BMC of 37 ppm to obtain P50 value of 51 ppm; P95/P50 ratio = BMC/BMCL. Since decreased traction time is a continuous endpoint, no factors for extrapolation to ED_{50} are applied.

Step 2: Application of interspecies (animal-to-human) adjustments

For interspecies (animal-to-human) adjustments, the IPCS methodology first considers a factor for body-size scaling ($AF_{Interspecies\text{-}BS}$), and then a factor for remaining toxicokinetic (TK) and toxicodynamic (TD) differences ($AF_{Interspecies\text{-}TK/TD}$). For inhalation studies, the IPCS P50 value for body-size scaling is equal to 1 / regional gas dose ratio (RGDR), and the P95/P50 value is equal to 2.[37] EPA applied a RGDR = 1,[38] therefore the P50 value in this case is 1.

For the TK/TD differences remaining after body size scaling, the IPCS report recommends a central estimate (P50) of 1 (i.e., no additional interspecies differences) and representing uncertainty with a P95/P50 factor of 3.[39] This recommendation corresponds to a default case in which EPA applies a residual interspecies uncertainty factor of 3 after applying the dosimetric adjustment based on the RGDR. For 1-BP, however, EPA applied an interspecies uncertainty factor (UF_A) of 10 after the dosimetric adjustment:

> an UF_A of 10 is retained to account for additional toxicokinetic differences that remain unaccounted for. 1-BP is irritating to the respiratory tract and rodents exhibit physiological responses (such as reflex bradypnea) that differ from humans and may alter uptake due to hyper- or hypoventilation, resulting in decreased internal dose in rodents relative to the applied concentration. Therefore, an UF_A of 10 is retained to account for toxicokinetic differences.[40]

[37] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.6.
[38] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), Table 3-2., note 4.
[39] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.3.
[40] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), pp. 214-215.

To account for EPA's interspecies adjustment in the IPCS framework, we similarly set the P95/P50 value for $AF_{Interspecies\text{-}TK/TD}$ equal to 10.

The interspecies adjustment factors are entered In the IPCS approximate probabilistic calculation template as follows:

Interspecies adjustments for probabilistic dose-response analysis of chronic oral exposure to 1-BP		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$[a]	1	2
$AF_{Interspecies\text{-}TK/TD}$[b]	1	10

[a] IPCS Table 4.6, incorporating EPA RGDR of 1.
[b] P95/P50 value of 10 corresponds to EPA's use of interspecies factor of 10, rather than 3, after application of body size default adjustment factor.

Step 3: Application of intraspecies (human variability) adjustments

In the IPCS methodology, the value of the human variability adjustment factor ($AF_{intraspecies}$) varies depending on the incidence of the adverse effect in the exposed population – with a larger adjustment factor necessary to extrapolate from the POD to lower levels of incidence. The IPCS report provides $AF_{intraspecies}$ for several incidence (I) values. The P50 and P95/P50 values for $AF_{intraspecies}$ provided by IPCS for several values of I, along with additional values of I of interest for this analysis, are provided in the following table:

Lognormal approximation of uncertainty distributions for intraspecies variability ($AF_{Intraspecies}$) for varying levels of population incidence (I)		
Incidence (I)	**$AF_{Intraspecies}$**	
	P50	**P95/P50**
10%[a]	3.49	2.24
5%[a]	4.98	2.82
1%[a]	9.69	4.32
0.5% (1-in-200)[a]	12.36	5.06
0.3% (1-in-333)[b]	14.61	5.64
0.1% (1-in-1,000)[a]	20.42	6.99
0.01% (1-in-10,000)[a]	37.71	10.39
0.001% (1-in-100,000)[b]	64.25	14.65

[a] IPCS Table 4.5

[b] Calculated for this analysis using the same methods that were used to derive IPCS Table 4.5

Step 4: Calculation of HD_M^I

The output of the IPCS methodology is generically described as an HD_M^I value – the human dose (HD) associated with a particular magnitude of effect M at a particular population incidence I. For this analysis, the "M" represents either decreased brain weight in adult F1 males or decreased traction time. The following tables present the calculation of HD_M^I for I = 1% and 0.1% using the POD, $AF_{Interspecies}$, and $AF_{intraspecies}$ values shown above. HD_M^I values for other levels of incidence can be determined by substituting the $AF_{intraspecies}$ values appropriate for each level of incidence into the tables below and then recalculating HD_M^I using the substituted $AF_{intraspecies}$.

The IPCS approach is a probabilistic method, so the HD_M^I is a distribution; selected values from that distribution are presented in the tables as follows:

- P05: 5th percentile estimate (lower confidence limit) of HD_M^I (this value is shown in **bold**)
- P50: 50th percentile estimate (median) of HD_M^I
- P95: 95th percentile estimate (upper confidence limit) of HD_M^I.

All HD_M^I values in the following tables are human equivalent concentration (HEC) 8-hour time-weighted averages, as they incorporate the same dosimetric and duration adjustments applied by EPA (see steps 1 and 2 above).

Calculation of HD_M^I from chronic 1-BP inhalation exposure: Decreased brain weight in adult F1 males (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
LOAEL	110 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5
IPCS POD = ED_{50}	**49.5 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	2
$AF_{Interspecies\text{-}TK/TD}$	1	10
$AF_{Intraspecies\ (I=1\%)}$	9.69	4.32
HD_M^I	5.1 ppm[a]	30.7[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.17 ppm**	157 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 2)^2 + (\log 10)^2 + (\log 4.32)^2]^{0.5}} = 30.7$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic 1-BP inhalation exposure: Decreased brain weight in adult F1 males (Incidence = 0.1%)		
Aspect	**P50**	**P95/P50**
LOAEL	110 ppm	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	10	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5
IPCS POD = ED_{50}	**49.5 ppm**	**7.02**
$AF_{Interspecies\text{-}BS}$	1	2
$AF_{Interspecies\text{-}TK/TD}$	1	10
$AF_{Intraspecies\ (I=0.1\%)}$	20.42	6.99
HD_M^I	2.4 ppm[a]	38.7[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.06 ppm**	94 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 2)^2 + (\log 10)^2 + (\log 6.99)^2]^{0.5}} = 38.7$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic 1-BP inhalation exposure: Decreased traction time (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
IPCS POD = BMC	**51 ppm**	**2.06**
$AF_{Interspecies\text{-}BS}$	1	2
$AF_{Interspecies\text{-}TK/TD}$	1	10
$AF_{Intraspecies\ (I=1\%)}$	9.69	4.32
HD_M^I	5.3 ppm[a]	18.3[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.29 ppm**	96 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 2.06)^2 + (\log 2)^2 + (\log 10)^2 + (\log 4.32)^2]^{0.5}} = 18.3$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I from chronic 1-BP inhalation exposure: Decreased traction time (Incidence = 0.1%)		
Aspect	**P50**	**P95/P50**
IPCS POD = BMC	**51 ppm**	**2.06**
$AF_{Interspecies-BS}$	1	2
$AF_{Interspecies-TK/TD}$	1	10
$AF_{Intraspecies\ (I=0.1\%)}$	20.42	6.99
HD_M^I	2.5 ppm[a]	23.9[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.10 ppm**	60 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b](Composite P95/P50) = $10^{[(\log 2.06)^2 + (\log 2)^2 + (\log 10)^2 + (\log 6.99)^2]^{0.5}} = 23.9$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Interpretation of Results

The National Academies and the WHO/IPCS have both recommended using the lower confidence limit (LCL) on a probabilistic dose-response distribution for use in decision-making, in place of a traditional reference dose (RfD) or reference concentration (RfC). The National Academies said in *Science and Decisions* that:

> Multiple risk-specific doses could be provided…in the various risk characterizations that EPA produces to aid environmental decision-making.[41]
>
> A Risk-Specific Reference Dose: For quantal effects, the RfD can be defined to be the dose that corresponds to a particular risk specified to be de minimis (for example, 1 in 100,000) at a defined confidence level (for example, 95%) for the toxicity end point of concern.[42]

The WHO/IPCS said:

> The LCL of the HD_M^I can be used as a probabilistic RfD to replace the deterministic RfD. In this case, the probabilistic RfD is the dose that protects the population from a specified magnitude and incidence of effect with a pre-specified per cent coverage (confidence).[43]

[41] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[42] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[43] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, p. 12.

Consistent with the guidance from the National Academies and the IPCS, we summarize the results of this analysis in the following table of the lower confidence limit (5th percentile or P05) risk-specific doses (HD_M^I) for multiple levels of risk (incidence or I), for both decreased brain weight in adult F1 males and decreased traction time.

Risk-specific dose estimates for chronic inhalation exposures to 1-BP for two selected non-cancer endpoints		
Incidence (I)	**HD_M^I lower -confidence limit (P05)**	
	Decreased brain weight in adult F1 males	**Decreased traction time**
5%	0.38 ppm	0.68 ppm
1%	0.17 ppm	0.29 ppm
0.5%	0.12 ppm	0.21 ppm
0.3% (1-in-333)[b]	0.10 ppm	0.17 ppm
0.1% (1-in-1,000)[a]	0.06 ppm	0.10 ppm
0.01% (1-in-10,000)	0.03 ppm	0.04 ppm
0.001% (1-in-100,000)	0.01 ppm	0.02 ppm

Based on application of the WHO/IPCS methodology to decreased brain weight in adult F1 males and decreased traction time from chronic exposure to 1-BP, we find that:

- 0.38 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 5% of the exposed population, and 0.68 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 5% of the exposed population.
- 0.17 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 1% of the exposed population, and 0.29 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 1% of the exposed population.
- 0.06 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 0.1% of the exposed population, and 0.10 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 0.1% of the exposed population.
- 0.03 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 0.01% (1-in-10,000) of the exposed population, and 0.04 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 0.01% (1-in-10,000) of the exposed population.

- 0.01 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased brain weight is expected in 0.001% (1-in-100,000) of the exposed population, and 0.02 ppm is the lower bound (95% confidence) chronic inhalation exposure at which decreased traction time is expected in 0.001% (1-in-100,000) of the exposed population.

The implications of these risk values can be understood by comparison with the exposure levels considered by EPA to represent negligible risk in the *Risk Evaluation for 1-Bromopropane* and comparison with EPA's proposed workplace exposure limit. The lowest non-cancer POD in EPA's risk evaluation is 17 ppm and has a benchmark MOE of 100,[44] meaning that EPA concludes for non-cancer outcomes that there are "negligible concerns for adverse human health effects"[45] for any 1-BP exposure below 0.17 ppm (17 ppm / 100 = 0.17 ppm). Our analysis indicates that an exposure of 0.17 ppm is equal to the lower-bound dose for the 1% (1-in-100) risk level for decreased brain weight, and is equal to the lower-bound dose for the 0.3% (1-in-333) risk level for decreased traction time. These risks far exceed EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[46]

EPA has proposed an existing chemical exposure limit (ECEL) of 0.05 ppm, which it says "represents the concentration at which an adult human, including a member of a PESS, would be unlikely to suffer adverse effects if exposed for a working lifetime" and "will eliminate any unreasonable risk of injury to health from occupational inhalation exposures."[47] Our analysis indicates that an exposure of 0.05 ppm is just below the lower-bound dose for the 0.1% (1-in-1,000) risk level for decreased brain weight, and is greater than the lower-bound dose for the 0.01% (1-in-10,000) risk level for decreased traction time. These risks also exceed EPA's usual target range of protection for carcinogenic risks of 1-in-10,000 to 1-in-1,000,000.[48]

The estimates of HD_M^I presented here were based entirely on input values and equations available from the WHO/IPCS methodology document and related publications, and from EPA's Risk Evaluation for 1-Bromopropane. An important caveat to these calculations is that the values used to represent human variability may be understated. The IPCS default human variability distribution is based on 37 data sets for human toxicokinetic variability and 34 data sets for human toxicodynamic variability. Most of these data sets were obtained from controlled human exposure studies of pharmaceuticals conducted in small samples of healthy adults, representing

[44] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), Table 3-2.
[45] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 243.
[46] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 320.
[47] 1-Bromopropane (1–BP); Regulation Under the Toxic Substances Control Act (TSCA). Proposed Rule. 89 FR 65066, August 8, 2024.
[48] U.S. EPA (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide), p. 320.

considerably less variability than found in the general population.[49,50,51] If human variability is underestimated, then the actual dose associated with each incidence level (e.g. I =1%, I = 0.1%) will be lower than the values obtained from this analysis – or in other words, risk at each dose will be underestimated.

[49] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

[50] Hattis, D., Lynch, M.K. (2007). Empirically observed distributions of pharmacokinetic and pharmacodynamic variability in humans—Implications for the derivation of single-point component uncertainty factors providing equivalent protection as existing reference doses. In Lipscomb, J.C. & Ohanian, E.V. (Eds.), *Toxicokinetics in risk assessment* (pp. 69-93). Taylor & Francis Group. https://doi.org/10.1201/b14275.

[51] Axelrad, D. A., Setzer, R. W., Bateson, T. F., DeVito, M., Dzubow, R. C., Fitzpatrick, J. W., Frame, A. M., Hogan, K. A., Houck, K., Stewart, M. (2019). Methods for evaluating variability in human health dose-response characterization. Hum Ecol Risk Assess, 25, 1-24. https://doi.org/10.1080/10807039.2019.1615828.