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Comments from Academics, Scientists and Clinicians on Proposed Low-Priority Substance Designation Under the Toxic Substances Control Act (TSCA)

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These comments are submitted on behalf of the undersigned academics, scientists, and clinicians. 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. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support.

We appreciate the opportunity to provide written comments on the proposed low priority chemical designations, issued under EPA's Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA").[1] A low priority designation is intended to identify chemicals with data sufficient to establish they are non-hazardous and safer— an important step in moving away from the use of dangerous or untested chemicals to safer chemicals, materials, products, and processes. Because EPA's low priority designations will give these chemicals a *de facto* 'safer' label, the production, use, and exposures to these low priority chemicals will likely expand in the future. Thus, it is critical that the low priority chemicals do not pose health hazards, including to potentially exposed and susceptible sub-populations.

The law recognizes the importance of comprehensively assessing a chemical before designating it as low priority. TSCA states that a low priority listing is appropriate for a substance for which "the Administrator concludes, based on information sufficient to establish…that such substance does not meet the standard" for a high-priority substance.[2] Therefore to designate a substance low priority, the Administrator must find that the chemical does not present unreasonable risks to health or the environment based on "sufficient information." Unfortunately, EPA's current proposed low priority designations do not meet this standard; the Agency has repeatedly categorized critical health endpoints for multiple chemicals as low hazard without sufficient information. This means that we cannot be confident the 20 proposed low priority chemicals are actually low hazard. As we have commented previously, EPA must gather additional data to support its low priority designations.[3,4,5,6]

[1] 84 FR 41712

[2] 15 USC §2605

[3] US EPA (2017). Procedures for Prioritization of Chemicals for Risk Evaluation under Toxic Substances Control Act; Comment submitted by J. Lam et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0636-0071

[4] US EPA (2018). Approaches for Identifying Potential Candidates for Prioritization for Risk Evaluation Under Amended TSCA; Notice of Public Meeting and Opportunity for Public Comment; Comment submitted by Veena Singla, PhD, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2017-0586-0077

[5] US EPA (2018). A Long-term Approach for Organizing the TSCA Chemical Inventory.; Comment submitted by Veena Single, PhD, Associate Director, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0659-0026

[6] US EPA (2019). Prioritization of Chemicals under TSCA; First Set of Candidate Chemical Substance; Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment Department of

Finally, TSCA requires that EPA use the best available science and the weight of scientific evidence to make decisions on chemicals, including low priority chemical designations.[7] The standards required for the science on low priority chemicals are no different than for any other decision under TSCA; yet, EPA has proposed an entirely new approach to data quality evaluation for the low priority chemicals that is inconsistent both with its previous approach and with established, peer-reviewed, validated methods for systematic review. EPA's approach does not follow current scientific principles nor the mandate of the law.

Our comments address the following main points:

1. **EPA has not established the suitability of the analog chemicals it selected to support low hazard determinations.**
2. **According to established authoritative guidelines, including EPA's own guidelines, EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for four endpoints: developmental toxicity, reproductive toxicity, carcinogenicity and endocrine activity. To meet the requirement of the law for sufficient evidence that these chemicals do not pose an unreasonable risk, EPA must obtain additional data.**
    a. **EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for developmental toxicity, including neurodevelopmental toxicity.**
    b. **EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for reproductive toxicity.**
    c. **EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for carcinogenicity.**
    d. **EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for endocrine activity.**
3. **EPA's approach for evaluating and integrating data on the low priority substances is not consistent with its previous approach or current empirically based approaches, and has not been peer-reviewed or validated.**

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

Sincerely,

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Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0131-0010

[7] 15 USC §2625 (h)-(i); Weight of the scientific evidence is defined in 40 CFR 702.33 as "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.''

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DETAILED COMMENTS

1. EPA has not established the suitability of the analog chemicals it selected to support low hazard determinations.

For many health and ecological endpoints, EPA uses data from analog chemicals as the sole evidence to support a low hazard determination. For example, for the human health endpoints of reproductive and/ or developmental toxicity and carcinogenicity EPA uses data from analogs in 15 of the 20 (75%) of the low priority support documents, as detailed in Appendix A.

For the selected analogs, EPA provides some version of the following justification in each support document:

> "EPA used best professional judgement to select analogs for [chemical] based on similarity in structure and functionality, with the assumption that these chemicals will have similar environmental transport and persistence characteristics, and bioavailability and toxicity profiles."[8]

However, EPA does not provide any further information on how it screened potential analogs, what criteria it used to ultimately select the analog it used, or data showing the selected analog is substantially similar to the low priority chemical. EPA states it selected analogs using "similarity in structure" but there are no details of how structural similarity was judged. Generally, chemical similarity analysis involves structural descriptors and similarity coefficient calculation, with the Tanimoto coefficient being widely used due to its utility and predictive accuracy.[9] The Tanimoto coefficient ranges from 0 to 1, with 0 being the least similar and 1 being the most similar. A Tanimoto coefficient of 0.8 or greater is often used to group similar chemicals, and this threshold was recently used by the National Academies to group analogs for flame retardant chemicals.[10] Calculation of Tanimoto coefficients for the low priority chemicals and EPA's selected analogs (see Appendix A) shows that most do not reach 0.8 and a number of them are very low, below 0.3. This raises serious concerns about whether the analogs

[8] See, for example, US EPA (2019). Dossier for Candidate Low-Priority Substance D-gluco-Heptonic acid, sodium salt (1:1), (2.xi.)- (CASRN 31138-65-5) (Sodium Glucoheptonate) pg. 21

[9] Chen, X., & Reynolds, C. H. (2002). Performance of similarity measures in 2D fragment-based similarity searching: Comparison of structural descriptors and similarity coefficients. *Journal of Chemical Information and Computer Sciences*, *42*(6), 1407–1414. https://doi.org/10.1021/ci025531g

[10] National Academies of Sciences Engineering and Medicine. (2019). A Class Approach to Hazard Assessment of Organohalogen Flame Retardants. In *A Class Approach to Hazard Assessment of Organohalogen Flame Retardants*. https://doi.org/10.17226/25412

EPA selected are in fact structurally similar to the low priority chemicals, and therefore calls into question the use of the analog data to draw conclusions of low hazard.

EPA also states that it assumed the analogs "will have similar environmental transport and persistence characteristics" to the low priority chemical but does not provide any data to support these assumptions, such as comparison of physicochemical properties or modeling outputs to show the chemical and analog are similar.

Without more quantitative and/ or supporting data to justify the similarity of the selected analogs, EPA has failed to show it has sufficient data to characterize the proposed low priority chemicals as low hazard.

2. According to established authoritative guidelines, including EPA's own guidelines, EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for four endpoints: developmental toxicity, reproductive toxicity, carcinogenicity and endocrine activity. To meet the requirement of the law for sufficient evidence that these chemicals do not pose an unreasonable risk, EPA must obtain additional data.

As detailed in Table 2 and Appendix B, most of the proposed low priority chemicals have major data gaps for the human health endpoints of reproductive/ developmental toxicity and carcinogenicity. EPA failed to assess endocrine activity, despite this being a critical hazard, especially to fetuses, infants, children and pregnant women—all susceptible sub-populations.[11, 12]

Table 2. Summary of data gaps for critical human health endpoints. (See Appendix A for detailed information)

Endpoint	**Data gaps**
Carcinogenicity	19/20 (95%) lack sufficient empirical data
Reproductive toxicity	20/20 (100%) lack sufficient empirical data
Developmental toxicity	18/20 (90%) lack sufficient empirical data
Endocrine activity	20/20 (100%) lack sufficient empirical data

(a) EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for developmental toxicity, including neurodevelopmental toxicity.

We have previously commented that EPA's Guidelines for Developmental Toxicity Risk Assessment note that, in general, short-term developmental toxicity tests (such as OECD 421) are not suitable for use in risk assessment.[13] Additionally, the Guidelines state:

[11] Diamanti-Kandarakis, E., Bourguignon, J.-P., Giudice, L. C., Hauser, R., Prins, G. S., Soto, A. M., … Gore, A. C. (2009). Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews*, *30*(4), 293–342. https://doi.org/10.1210/er.2009-0002

[12] Gore, A. C., Chappell, V. A., Fenton, S. E., Flaws, J. A., Nadal, A., Prins, G. S., … Zoeller, R. T. (2015). Executive Summary to EDC-2: The Endocrine Society's second Scientific Statement on endocrine-disrupting chemicals. *Endocrine Reviews*, *36*(6), 593–602. https://doi.org/10.1210/er.2015-1093

[13] US EPA (2019). Initiation of Prioritization Under the Toxic Substances Control Act (TSCA); Comment submitted by Veena Singla, PhD, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D= EPA-HQ-OPPT-2019-0131, EPA–HQ–OPPT–2018–0476, and EPA–HQ–OPPT–2018–0462

> "The minimum evidence needed to judge that a potential hazard does not exist would include data from appropriate, well-conducted laboratory animal studies in several species (at least two) which evaluated a variety of the potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to the adult."[14]

Therefore, EPA requires data from well-conducted studies in at least two animal species to make a determination that a candidate chemical poses low hazard for developmental toxicity. According to the Guidelines, 18 of the 20 proposed low priority chemicals do not have sufficient evidence to establish low developmental toxicity (see Appendix A).

For example, in the Support Document for Proposed Designation of 1-Butanol, 3-Methoxy-, 1-Acetate, the evidence EPA used to determine low concern for developmental toxicity is:

> "EPA assessed the potential for mammalian developmental toxicity by 3-methoxybutyl acetate using an OECD Guideline 414 study in rats exposed via oral gavage during gestation days 7-16 (ECHA, 1997b). No maternal or fetal toxicity was observed at the single dose tested (1000 mg/kg-day), resulting in a NOAEL of 1000 mg/kg-day. This result, taken with the low-concern criteria oral threshold of 250 mg/kg-day, indicate low-concern for developmental toxicity."[15]

But this evidence does not meet EPA's Guidelines as it:

- is only from a single species;
- is not a "well-conducted study" (OECD 414 Guideline states: "At least three dose levels and a concurrent control should be used,"[16] but only a single dose was tested.)
- does not cover a "variety of the potential manifestations of developmental toxicity," especially neurodevelopmental toxicity. (OECD 414 Guideline states: "Functional deficits, although an important part of development, are not a part of this Guideline. They may be tested for in a separate study or as an adjunct to this study using the Guideline for developmental neurotoxicity."[17])

Therefore, according to its own Guidelines, EPA does not have sufficient evidence that 1-Butanol, 3-methoxy-, 1-acetate poses a low hazard for developmental toxicity. Of the proposed low priority chemicals, only glucono-delta lactone (90-80-2) and dipropylene glycol (24800-44-0) potentially have sufficient evidence to make a determination on developmental toxicity; however, the evidence needs to be evaluated using a valid systematic review method as detailed in point 3 below.

Neurodevelopmental Toxicity

EPA does not have sufficient data to determine a low hazard for neurodevelopmental toxicity for any of the proposed low priority chemicals.

In collaboration with Health Canada, EPA published an updated Developmental Neurotoxicity (DNT) guidance document on "the review and interpretation of submitted DNT data to provide guidance on

[14] US EPA (Dec 1991) Guidelines for Developmental Toxicity Risk Assessment. Pp. 40.

[15] US EPA (2019). Dossier for Candidate Low-Priority Substance 1-Butanol, 3-methoxy-, 1-acetate(CASRN 4435-53-4)(3-Methoxybutyl Acetate) Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2019-0106D =EPA-HQ-OPPT-2019-0106

[16] OECD (2018) Test No. 414: Prenatal Developmental Toxicity Study. Pg. 3. Available: https://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study_9789264070820

[17] Id. Pg. 1.

how to evaluate the quality, the conduct, and resulting data derived from the behavioral methods employed in the OECD and/or EPA DNT Guidelines." [18] The document describes modules including detailed clinical observations, motor activity, acoustic/ auditory startle response, and learning and memory data, which should all be included in a comprehensive evaluation of DNT.

In addition to using the Guidelines for Developmental Toxicity Risk Assessment referenced above, EPA should request data needed according to the updated EPA DNT guidance to make a determination on neurodevelopmental toxicity for each of the proposed low priority chemicals.

(b) EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for reproductive toxicity.

We have previously commented that EPA's Guidelines for Reproductive Toxicity Risk Assessment note that a prolonged treatment period is required to assess reproductive effects and that screening tests limited to one generation are not suitable for risk assessment.[19,20] Additionally, the Guidelines state:

> "The minimum evidence needed to determine that a potential hazard does not exist would include data on an adequate array of endpoints from more than one study with two species that showed no adverse reproductive effects at doses that were minimally toxic in terms of inducing an adverse effect." [21]

According to these criteria, none of the 20 proposed low priority chemicals have sufficient evidence to establish low reproductive toxicity hazard. For example, in the Support Document for Proposed Designation of 1-Butanol, 3-Methoxy-, 1-Acetate, the evidence used to determine low concern for reproductive toxicity is:

> "Although reproductive toxicity data is unavailable, EPA considers concern for this endpoint to be low based on the low-hazard findings for other mammalian endpoints, including but not limited to acute toxicity, repeated dose toxicity, and developmental toxicity."[22]

This clearly does not meet EPA's Guidelines as there is no empirical data on 1-Butanol, 3-Methoxy-, 1-Acetate's reproductive toxicity.

[18] NAFTA Technical Working Group on Pesticides. (2016) Developmental Neurotoxicity Study Guidance Document. Pg. 3. Available: https://www.epa.gov/sites/production/files/2017-02/documents/developmental_neurotoxicity_study_internal_guidance_document_final_0.pdf

[19] US EPA (Oct 1996) Guidelines for Reproductive Toxicity Risk Assessment. Pp. 7 Available: https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf

[20] US EPA (2019). Prioritization of Chemicals under TSCA; First Set of Candidate Chemical Substance; Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0131-0010

[21] Id. pp. 72

[22] US EPA (2019). Dossier for Candidate Low-Priority Substance 1-Butanol, 3-methoxy-, 1-acetate(CASRN 4435-53-4)(3-Methoxybutyl Acetate) Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2019-0106D =EPA-HQ-OPPT-2019-0106

(c) EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for carcinogenicity.

We have previously commented that EPA's Guidelines for Carcinogen Risk Assessment state that a determination of "Not Likely to Be Carcinogenic to Humans" requires robust evidence:[23]

> "based on data such as:
>
> - animal evidence that demonstrates lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects),
> - convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans,
> - convincing evidence that carcinogenic effects are not likely by a particular exposure route (see Section 2.3), or
> - convincing evidence that carcinogenic effects are not likely below a defined dose range.
>
> A descriptor of "not likely" applies only to the circumstances supported by the data." [24]

According to these criteria, 19 of the 20 proposed low priority chemicals do not have sufficient evidence to establish low concern for carcinogenicity. For example, in the Support Document for Proposed Designation of 1-Butanol, 3-Methoxy-, 1-Acetate the evidence used to determine low concern for carcinogenicity is:

> "Because quality experimental data on 3-methoxybutyl acetate were limited, EPA relied on publicly available quantitative structure activity relationship (QSAR) models and structural alerts (SA) to assess the carcinogenic potential for 3-methoxybutyl acetate…. 3-Methoxybutyl acetate's expected metabolism, lack of structural alerts, and negative genotoxicity results indicate that this chemical is unlikely to be carcinogenic or mutagenic."[25]

This clearly does not meet EPA's Guidelines as no empirical data is available on 3-Methoxybutyl acetate's carcinogenicity. Of the proposed low priority chemicals, only dipropylene glycol potentially has sufficient evidence to make a determination on carcinogenicity; however, the evidence needs to be evaluated using a valid systematic review method as detailed in point 3 below.

(d) EPA does not have sufficient evidence to establish that the proposed low priority chemicals have low hazard for endocrine activity.

EPA did not evaluate endocrine activity for any of the proposed low priority chemicals. ECHA's guidance for the identification of endocrine disruptors describes the data set sufficient to support the absence of

[23] US EPA (2019). Prioritization of Chemicals under TSCA; First Set of Candidate Chemical Substance; Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0131-0010

[24] US EPA (2005) Guidelines for Carcinogen Risk Assessment. Pp. 84-85. Available from: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

[25] US EPA (2019). Dossier for Candidate Low-Priority Substance 1-Butanol, 3-methoxy-, 1-acetate(CASRN 4435-53-4)(3-Methoxybutyl Acetate) Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2019-0106D =EPA-HQ-OPPT-2019-0106

adverse effects on estrogenic, androgenic, thyroidal and steroidogenic modalities (EATS). [26] The dataset includes:

- For estrogenic, androgenic and steroidogenic modalities: Extended one-generation reproductive toxicity study (OECD TG 443; with cohort 1a/1b including the mating of cohort 1b to produce the F2 generation)[27] or a two-generation reproductive toxicity study (OECD TG 416; test protocol according to latest version of January 2001)[28]
- For thyroidal modalities: OECD test guidelines 407, 408, 409 (and/or the one-year dog study, if available), 416 (or 443 if available) and 451-3 with thyroid parameters included.

To determine that a proposed low priority chemical poses low concern for endocrine activity, EPA needs data as described by ECHA to demonstrate a lack of adverse endocrine effects.

Overall, to fulfill the mandate of the law and appropriately designate non-hazardous low priority chemicals, EPA must gather additional data to ensure the proposed chemicals actually are low hazard for critical human health endpoints, using established criteria from its own Guidelines and other authoritative guidelines.

3. EPA's approach for evaluating and integrating data on the low priority substances is not consistent with its previous approach or current empirically based approaches, and has not been peer-reviewed or validated.

The 'Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA' states:

> "EPA's proposed priority designations under 40 CFR section 702.9 and final priority designations under 40 CFR section 702.11 will be consistent with the scientific standards provision in 15 U.S.C. 2625(h) and the weight of the scientific evidence provision in 15 U.S.C. 2625(i)." [29]

However, there are two major problems with EPA's general approach to the science on the low priority chemicals. First, EPA has changed the definition it is using for "weight of the scientific evidence," and the new definition is inconsistent both with its previous definition and with currently accepted scientific standards for integrating data to inform an overall conclusion. Second, EPA has changed its criteria for evaluating data quality, and the new criteria are inconsistent with its previous criteria and with established, peer-reviewed methods for evaluating study quality. There is little information in the Approach Document about the development process or rationale for the new criteria or definition. EPA's low priority methods are ad hoc, non-transparent and inconsistent with the Agency's mandate.

Weight of the Scientific Evidence

EPA has codified a definition of "weight of the scientific evidence" in its risk evaluation rule, which is:

[26] ECHA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. Pg. 31-32. Available: https://www.efsa.europa.eu/en/efsajournal/pub/5311

[27] OECD (2012) Test No. 443: Extended One-Generation Reproductive Toxicity Study. In: OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. 25 pp. https://doi.org/10.1787/9789264185371-en

[28] OECD (2001) Test No. 416: Two-Generation Reproduction Toxicity. In: OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. 13 pp. https://doi.org/10.1787/9789264070868-en

[29] EPA (2019) Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA. EPA Document ID No. 740B19008. Office of Pollution Prevention and Toxics. Washington, DC. Pg 13.

> "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.'' [30]

The Low Priority Approach Document proposes a new definition of "weight of the scientific evidence (WoSE)":

> "WoSE analysis is an integrative and interpretive process that considers information in favor (e.g., positive study) or against (e.g., negative study) a given hypothesis within the context of the assessment question(s) being evaluated." [31]

These two definitions are incompatible, as EPA's regulation requires using a systematic review method. Further, the National Academies strongly endorsed established systematic review methods for chemical evaluations as the best available science to comprehensively, transparently, and accurately evaluate the science and draw conclusions.[32]

Empirically based best practices for evidence integration and hazard determinations have been developed, peer-reviewed, validated and demonstrated, including by the National Toxicology Program,[33] the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method,[34] and the Navigation Guide.[35] We strongly recommend that EPA use one of these validated approaches to review and integrate the evidence into the final conclusions for each of the Low Priority Candidates.

Data Quality Criteria

EPA states that it developed a 'unique set of metrics' to evaluate data on the low priority candidates:

> "The quality of individual studies was assessed at the data evaluation stage in the screening review of low-priority substance candidates. For each on-topic study, EPA applied a data quality check using metrics most appropriate for low-hazard chemicals. EPA observed that low-priority substance candidates had fewer peer-reviewed data but had a greater number of grey literature and other sources as compared to chemicals with known hazards, so information from both sources were weighed equally in accordance with TSCA 26(i). Given these differences in information availability, data quality metrics were chosen to capture information from peer-reviewed and grey literature sources for evaluation of low-priority substance candidates."[36]

[30] 40 CFR 702.33

[31] Id. Pg 13

[32] The National Academies of Sciences. (2017). *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*. https://doi.org/10.17226/24758

[33] National Toxicology Program Office of Health Assessment and Translation. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Institute of Environmental Health Sciences; 2015

[34] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026

[35] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014.

[36] Id. pg. 11

It is unclear what is meant by "metrics most appropriate for low-hazard chemicals;" there is no *a priori* reason that quality of the evidence on a low hazard chemical would differ from a hazardous chemical. The law requires 'sufficient evidence' to establish low hazard, and the 'best available science'—this means that EPA must use quality data, as delineated by current science, to inform its low priority decisions. It appears that EPA created the new metrics due to a lack of available high quality data. This is not allowed under the law and instead EPA should request the data it needs using the TSCA authorities given it by Congress.

In its previous TSCA evaluations, EPA used the metrics in 'Application of Systematic Review in TSCA Risk Evaluations' to evaluate data quality. We have detailed the scientific flaws in the TSCA systematic review method in numerous other comments to EPA and a peer-reviewed commentary,[37] so we are not endorsing that EPA should use this method. Rather, we wish to simply point out that the creation of an ad hoc method for the low priority chemicals is inconsistent with the approach that EPA has been using, and EPA has not explained why it would *not* apply its former approach to the low priority chemicals.

Finally, the new data quality evaluation domains and metrics appear arbitrary as they are different from EPA's TSCA method and established systematic review methods, and there is no information on how the new domains/metrics were developed. The new metrics include a variety of items that do not empirically affect risk of bias, such as reporting.

This leads to two major problems. One, EPA likely eliminated relevant science because it applied these arbitrary criteria and "excluded references with unacceptable data quality."[38] Two, the studies EPA relied on to make its low priority determinations have not been appropriately evaluated, so we do not know the overall quality of the evidence base for each chemical nor how confident we can be in EPA's conclusions.

It is vital to the integrity of any evidence-based evaluation of environmental health, regardless of whether the assessment uses systematic review methods or not, that the included studies used in the regulatory decision-making processes are assessed with transparent and scientifically accepted methods. We therefore recommend EPA use either of two previously validated methods, the Navigation Guide[39] or the Office of Health Assessment and Translation,[40] to assess the quality of the evidence before making final determinations on a chemical's hazards.

[37] Singla, V. I., Sutton, P. M., & Woodruff, T. J. (2019). The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health. *American Journal of Public Health*, *109*(7), 982–984. https://doi.org/10.2105/AJPH.2019.305068

[38] EPA (2019) Approach Document for Screening Hazard Information for Low-Priority Substances Under TSCA. EPA Document ID No. 740B19008. Office of Pollution Prevention and Toxics. Washington, DC. Pg 10.

[39] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014.

[40] National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program; 2015.

Appendices:

Appendix A. Tanimoto similarity coefficients for proposed low priority chemicals and analogs for which EPA used analog data to designate low hazard for reproductive toxicity, developmental toxicity and/ or carcinogenicity.

Appendix B. Low priority hazard ratings for proposed low priority chemicals with recommendations

Appendix A. Tanimoto similarity coefficients for proposed low priority chemicals and analogs for which EPA used analog data to designate low hazard for reproductive toxicity, developmental toxicity and/ or carcinogenicity.

Tanimoto similarity coefficients were calculated by using the PubChem Compound Identifier (CID) as input into the Similarity Workbench of ChemMine Tools.[1]

AP Tanimoto is the Tanimoto coefficient calculated using an atom pair algorithm as described by Chen and Reynolds, 2002.[2]

MCS Tanimoto is the Tanimoto coefficient calculated using a Maximum Common Substructure algorithm as described by Cao, 2008.[3]

Number in FR notice	**Proposed low priority chemical name (CAS RN)**	**Name of analog(s) in support document (CAS RN)** ***Endpoint(s) for which analog data was used***	**AP Tanimoto**	**MCS Tanimoto**
2	D-gluco-Heptonic acid, sodium salt (31138-65-5) PubChem CID: 49853507	D-Gluconic acid, .delta.-lactone; Glucono-delta-lactone (90-80-2) *Developmental tox* PubChem CID: 7027	0.401639	0.6471
3	D-Gluconic acid (526-95-4) Pubchem CID: 10690	D-gluco-Heptonic acid, sodium salt (31138-65-5) *Reproductive/ developmental tox* PubChem CID: 49853507	0.71028	0.8125
		D-Gluconic acid, .delta.-lactone; Glucono-delta-lactone (CAS RN 90-80-2) *Developmental tox* PubChem CID: 7027	0.515789	0.7857
4	D-Gluconic acid, calcium salt, (299-28-5) Pubchem CID: 9290	D-gluco-Heptonic acid, sodium salt (31138-65-5) *Reproductive/ developmental tox* PubChem CID: 49853507	0.553571	0.4333
		D-Gluconic acid, .delta.-lactone; Glucono-delta-lactone (CAS RN 90-80-2) *Developmental tox* PubChem CID: 7027	0.313609	0.3929
5	D-Gluconic acid, .delta.-lactone; Glucono-delta-lactone (90-80-2)	D-gluco-Heptonic acid, sodium salt (31138-65-5) *Reproductive/ developmental tox*	0.401639	0.6471

[1] http://chemminetools.ucr.edu/

[2] Chen, X., & Reynolds, C. H. (2002). Performance of similarity measures in 2D fragment-based similarity searching: Comparison of structural descriptors and similarity coefficients. *Journal of Chemical Information and Computer Sciences*, *42*(6), 1407–1414. https://doi.org/10.1021/ci025531g

[3] Cao, Y., Jiang, T., & Girke, T. (2008). A maximum common substructure-based algorithm for searching and predicting drug-like compounds. *Bioinformatics*, *24*(13), 366–374. https://doi.org/10.1093/bioinformatics/btn186

Number in FR notice	Proposed low priority chemical name (CAS RN)	Name of analog(s) in support document (CAS RN) *Endpoint(s) for which analog data was used*	AP Tanimoto	MCS Tanimoto
	PubChem CID: 7027	PubChem CID: 49853507		
6	D-Gluconic acid, potassium salt (299-27-4) Pubchem CID: 16760467	D-gluco-Heptonic acid, sodium salt (31138-65-5) *Reproductive/ developmental tox* PubChem CID: 49853507	0.71028	0.7647
		D-Gluconic acid, .delta.-lactone; Glucono-delta-lactone (CAS RN 90-80-2) *Developmental tox* PubChem CID: 7027	0.515789	0.7333
7	D-Gluconic acid, sodium salt (1:1) (527-07-01) Pubchem CID: 23672301	D-gluco-Heptonic acid, sodium salt (31138-65-5) *Reproductive/ developmental tox* PubChem CID: 49853507	0.71028	0.7647
		D-Gluconic acid, .delta.-lactone; Glucono-delta-lactone (CAS RN 90-80-2) *Developmental tox* PubChem CID: 7027	0.515789	0.7333
8	Decanedioic acid, 1,10-dibutyl ester (109-43-3) Pubchem CID: 7986	Dibutyl adipate (105-99-7) *Reproductive/ developmental tox* Pubchem CID: 7784	0.505882	0.4286
10	1-Eicosanol (629-96-9) Pubchem CID: 12404	1-Docosanol (661-19-8) *Reproductive/ developmental tox* Pubchem CID: 12620	0.822835	0.9130
		1-Octadecanol (112-92-5) *Reproductive/ developmental tox* Pubchem CID: 8221	0.805687	0.9048
13	Propanol, [2-(2-butoxymethylethoxy)methylethoxy] (55934-93-5) Pubchem CID: 22495263	Dipropylene glycol monobutyl ether (30025-38-8) *Reproductive tox* Pubchem CID: 57357911	0.281879	0.2727
		Tripropylene glycol monomethyl ether (20324-33-8) *Developmental tox* Pubchem CID: 30111	0.427673	0.7222
		Tripropylene glycol methyl ether (25498-49-1) *Developmental tox* Pubchem CID: 25054	0.621429	0.8235
		Dipropylene glycol methyl ether (34590-94-8) *Developmental tox* Pubchem CID: 22833331	0.222973	0.2857
14	Propanedioic acid, 1,3-diethyl ester; Diethyl Malonate (105-53-3)	Dimethyl malonate (108-59-8) *Reproductive tox* Pubchem CID: 7943	0.3	0.8182

Number in FR notice	Proposed low priority chemical name (CAS RN)	Name of analog(s) in support document (CAS RN) *Endpoint(s) for which analog data was used*	AP Tanimoto	MCS Tanimoto
	Pubchem CID: 7761	Dimethyl glutarate, CAS RN 1119-40-0 *Developmental tox* Pubchem CID: 14242	0.208971	0.3750
15	Propanedioic acid, 1,3-dimethyl ester; Dimethyl Malonate DMM (108-59-8) Pubchem CID: 7943	Dimethyl glutarate (1119-40-0) *Developmental tox* Pubchem CID: 14242	0.28169	0.4286
16	Propanol, 1(or 2)-(2-methoxymethylethoxy)-, acetate; DPMA (88917-22-0) Pubchem CID: 9815489	Dipropylene glycol monobutyl ether (30025-38-8) *Reproductive tox* Pubchem CID: 57357911	0.176991	0.3333
		Tripropylene glycol monomethyl ether (20324-33-8) *Developmental tox* Pubchem CID: 30111	0.362903	0.8000
		Tripropylene glycol methyl ether (25498-49-1) *Developmental tox* Pubchem CID: 25054	0.362903	0.6875
		Dipropylene glycol methyl ether (34590-94-8) *Developmental tox* Pubchem CID: 22833331	0.194175	0.3529
17	Propanol, [(1-methyl-1,2-ethanediyl)bis(oxy)]bis-; Tripropylene glycol (24800-44-0) Pubchem CID: 32611	Dipropylene glycol (25265-71-8) *Carcinogenicity, Developmental tox* Pubchem CID: 32881	0.443038	0.6923
18	2-Propanol, 1,1'-oxybis- (110-98-5) Pubchem CID: 8087	Dipropylene glycol (25265-71-8) *Carcinogenicity, Developmental tox* Pubchem CID: 32881	0.333333	0.8000
		Tripropylene glycol (24800-44-0) *Reproductive tox* Pubchem CID: 32611	0.212766	0.5714
19	Propanol, oxybis-; Oxydipropanol; Dipropylene glycol (25265-71-8) Pubchem CID: 32881	Tripropylene glycol (24800-44-0) *Reproductive tox* Pubchem CID: 32611	0.443038	0.6923

Appendix B. Low priority hazard ratings for proposed low priority chemicals with recommendations

Contents

1. 1-Butanol, 3-methoxy-, 1-acetate, CAS RN 4435-53-4

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	3-Methoxybutyl acetate's expected metabolism, lack of structural alerts, and negative genotoxicity results indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	Although reproductive toxicity data is unavailable, EPA considers concern for this endpoint to be low based on the low-hazard findings for other mammalian endpoints, including but not limited to acute toxicity, repeated dose toxicity, and developmental toxicity.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment.
Developmental toxicity	Low	EPA assessed the potential for mammalian developmental toxicity by 3-methoxybutyl acetate using an OECD Guideline 414 study in rats exposed via oral gavage during gestation days 7-16 (ECHA, 1997b). No maternal or fetal toxicity was observed at the single dose tested (1000 mg/kg-day), resulting in a NOAEL of 1000 mg/kg-day. This result, taken with the low-concern criteria oral threshold of 250 mg/kg-day, indicate low-concern for developmental toxicity.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested) Further, the OECD 414 Guideline states "At least three dose levels and a concurrent control should be used,"[1] but only a single dose was tested.
Neurodevel. toxicity	NA	Not rated	Data gap	OECD 414 does not assess neurodevelopmental toxicity. "Functional deficits, although an important part of development, are not a part of this Guideline. They may be tested for in a separate study or as an adjunct to this study using the Guideline for developmental neurotoxicity."[2]

[1] OECD (2018) Test No. 414: Prenatal Developmental Toxicity Study. Pg. 3. Available: https://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study_9789264070820

[2] OECD (2018) Test No. 414: Prenatal Developmental Toxicity Study. Pg. 1. Available: https://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study_9789264070820-en

2. D-gluco-Heptonic acid, sodium salt, CAS RN 31138-65-5

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Sodium glucoheptonate's metabolism, a lack of structural alerts, and experimental genotoxicity studies indicates that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	In the previously mentioned OECD Guideline 422 oral gavage study on rats (Section 6.1.3), no adverse reproductive effects were noted at the highest dose, resulting in a NOAEL of 1000 mg/kg-day. The study also examined a subset of developmental endpoints, such as litter parameters and assessment of surface righting reflexes. No adverse effects were noted for these developmental endpoints (ECHA, 2013e).	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment and Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested) Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[3]
Developmental toxicity	Low		Data gap	
Neurodevel. toxicity	NA	Not rated	Data gap	

[3] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

3. D-Gluconic acid, CAS RN 526-95-4

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	D-Gluconic acid is a multi-hydroxy acid that is likely to be metabolized through oxidation. D-Gluconic acid's metabolism, lack of structural alerts, and experimental genotoxicity studies indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for mammalian reproductive and developmental toxicity for D-gluconic acid using read-across from sodium glucoheptonate. An OECD Guideline 422 study exposed rats to sodium glucoheptonate by oral gavage beginning two weeks prior to mating and continued the exposure through gestation to lactation day 5 (for females) (ECHA, 2013a). No adverse reproductive effects were noted at the highest dose (1000 mg/kg-day), resulting in a NOAEL of 1000 mg/kg-day. The study also examined a subset of developmental endpoints, such as litter parameters and assessment of surface righting reflexes. No adverse effects were noted for these developmental endpoints.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment and Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested) Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[4]
Developmental toxicity	Low		Data gap	
Neurodevel. toxicity	NA	Not rated	Data gap	

[4] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

4. D-Gluconic acid, calcium salt, CAS RN 299-28-5

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Calcium gluconate's metabolism, lack of structural alerts, and experimental genotoxicity studies indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for mammalian reproductive and developmental toxicity for calcium gluconate using read-across from analogs. An OECD Guideline 422 study exposed female rats to sodium glucoheptonate by oral gavage beginning two weeks prior to mating and continued the exposure through gestation to lactation day 5 (Harlan Laboratories, 2013). No adverse reproductive effects were noted at the highest dose (1000 mg/kg-day), resulting in a NOAEL of 1000 mg/kg-day. The study also examined a subset of developmental endpoints, such as litter parameters and assessment of surface righting reflexes. No adverse effects were noted for these developmental endpoints.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment and Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested) Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[5]
Developmental toxicity	Low		Data gap	
Neurodevel. toxicity	NA	Not rated	Data gap	

[5] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

5. D-Gluconic acid, .delta.-lactone; (Glucono-delta-lactone), CAS RN 90-80-2

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Glucono-delta-lactone's metabolism, lack of structural alerts, and experimental genotoxicity studies suggest that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA further assessed the potential for reproductive and developmental toxicity for glucono-delta-lactone using read-across from sodium glucoheptonate. An OECD Guideline 422 oral gavage study exposed rats to sodium glucoheptonate beginning two weeks prior to mating and continued the exposure through gestation to lactation day 5 (for females), for a total of 8 weeks (ECHA, 2013). No adverse reproductive effects were noted at the highest dose, resulting in a NOAEL of 1000 mg/kg-day. The study also examined a subset of developmental endpoints, such as litter parameters and assessment of surface righting reflexes. No adverse effects were noted for these developmental endpoints.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species tested) Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[6]
Developmental toxicity	Low	EPA examined the potential for developmental toxicity using data from oral gavage studies on several species, including mice (JECFA, 1986; ECHA, 1973b; Inc, 1973), hamsters (JECFA, 1986; ECHA, 1979a; Inc, 1973), rabbits (JECFA, 1986; ECHA, 1973c; Inc, 1973), and rats (JECFA, 1986; ECHA, 1973a; Inc, 1973). These studies indicated no adverse effects at the highest dose of glucono-delta-lactone tested in each study, which ranged from 560 to 780 mg/kg-day.	Low	Sufficient experimental data to show low hazard as required by EPA's Guidelines for Developmental Toxicity Risk Assessment, provided the studies referenced are high quality when evaluated by a validated systematic review method.
Neurodevel. toxicity	NA	Not rated	Data gap	EPA should clarify whether neurodevelopmental endpoints were assessed in the available experimental data.

[6] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

6. D-Gluconic acid, potassium salt, CAS RN 299-27-4

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Potassium gluconate's metabolism, lack of structural alerts, and experimental genotoxicity studies indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for reproductive and developmental mammalian toxicity for potassium gluconate using read-across from sodium glucoheptonate. An OECD Guideline 422 oral gavage study exposed female rats to sodium glucoheptonate beginning two weeks prior to mating and continued the exposure through gestation to lactation day 5 (Harlan Laboratories, 2013). No adverse reproductive effects were noted at the highest dose (1000 mg/kg-day), resulting in a NOAEL of 1000 mg/kg-day. The study also examined a subset of developmental endpoints, such as litter parameters and assessment of surface righting reflexes. No adverse effects were noted for these developmental endpoints.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment and Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested) Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[7]
Developmental toxicity	Low		Data gap	
Neurodevel. toxicity	NA	Not rated	Data gap	

[7] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

7. D-Gluconic acid, sodium salt (1:1), CAS RN 527-07-01

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Sodium gluconate's endogenous nature, metabolism, a lack of structural alerts, and experimental genotoxicity studies indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for mammalian reproductive and developmental toxicity from sodium gluconate using read-across from sodium glucoheptonate. An OECD Guideline 422 study exposed rats to sodium glucoheptonate by oral gavage beginning two weeks prior to mating and continued the exposure through gestation to lactation day 5 (for females). No adverse reproductive effects were noted at the highest dose, resulting in a NOAEL of 1000 mg/kg-day (ECHA, 2013a). The study also examined a subset of developmental endpoints, such as litter parameters and assessment of surface righting reflexes. No adverse effects were noted for these developmental endpoints.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment and Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested) Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[8]
Developmental toxicity	Low		Data gap	
Neurodevel. toxicity	NA	Not rated	Data gap	

[8] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

8. Decanedioic acid, 1,10-dibutyl ester, CAS RN 109-43-3

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	EPA assessed the potential for dibutyl sebacate to cause carcinogenicity using experimental data. Rats exposed to dibutyl sebacate orally for two years demonstrated no cancer-related effects at the highest dose tested of 4400 mg/kg-day, resulting in a negative finding for carcinogenicity (Smith, 1953).	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment. (only 1 species tested)
Reproductive toxicity	Low	EPA assessed the potential for mammalian reproductive toxicity using read-across from dibutyl adipate. Rats exposed to dibutyl adipate by oral gavage beginning two weeks prior to mating and through day 3 of lactation (for females) displayed no effects on reproductive parameters, resulting in a NOAEL of 1000 mg/kg-day (OECD, 1996). This study also examined a subset of developmental parameters, including pup number, pup sex ratio, live and dead pups, postnatal deaths, gross abnormalities, pup weight gain, physical and behavioral abnormalities, reflexology and gross necropsy. No adverse effects were noted at the highest dose tested (1000 mg/kg-day), resulting in a NOAEL of 1000 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species tested)
Developmental toxicity	Low		Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested)
Neurodevel. toxicity	NA	Not rated	Data gap	

9. 1-Docosanol, CAS RN 661-19-8

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Because of the chemical's predictive metabolism, absence of genotoxicity in experimental studies, and low concern from predictive modeling, 1-docosanol has low concern for carcinogenicity.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for mammalian reproductive toxicity from 1-docosanol using experimental data. Rats exposed to 1-docosanol by oral gavage for 71 days total, beginning during premating and extending through mating for males and beginning 15 days premating and extending through gestation day (GD) 20 for females (OECD, 2006; Iglesias et al., 2002c; U.S. EPA, 2002d). This study reported no adverse effects, resulting in a NOAEL of 1000 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species tested)
Developmental toxicity	Low	EPA also assessed the potential for mammalian developmental toxicity from 1-docosanol using experimental data. A study on rabbits exposed to 1-docosanol by oral gavage during GD 6-19 reported a NOAEL of 2000 mg/kg-day (OECD, 2006; Iglesias et al., 2002c). Rats exposed to 1-docosanol by oral gavage for 71 days total, beginning during premating and extending through mating for males and beginning 15 days during premating and extending through GD 20 for females (OECD, 2006; Iglesias et al., 2002c; U.S. EPA, 2002d). This study reported no adverse developmental effects, resulting in a NOAEL of 1000 mg/kg-day.	Low	Sufficient experimental data to show low hazard as required by EPA's Guidelines for Developmental Toxicity Risk Assessment, provided the studies referenced are high quality when evaluated by a validated systematic review method.
Neurodevel. toxicity	NA	Not rated	Data gap	EPA should clarify whether neurodevelopmental endpoints were assessed in the available experimental data.

10. 1-Eicosanol, CAS RN 629-96-9

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	For this chemical, there is an absence of the types of reactive structural features that are present in genotoxic carcinogens. 1-Eiconsaol is not an electrophile. Further, predictions from the Virtual models for property Evaluation of chemicals within a Global Architecture (VEGA) models' indicate 1-eicosanol has a low potential to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for reproductive toxicity by 1-eicosanol using read-across from 1-docosanol and 1-octadecanol. Rats exposed to 1-docosanol by oral gavage for 71 days during premating through mating (males) or from 15 days premating through gestation day (GD) 20 (females) (OECD, 2006; Iglesias et al., 2002c; U.S. EPA, 2002d). This study reported no adverse effects, resulting in a NOAEL of 1000 mg/kg-day. In a combined repeated dose, reproductive, and developmental toxicity OECD Guideline 422 study, rats were exposed to 1-octadecanol in their diet for 45 days (males) to 54 days (females). Endpoints evaluated include mortality, clinical signs, body weight, food consumption, estrous cycles, ovary weight and histology, testes and epididymis weight and histology, pregnancy rate, gestation length, implantations, corpora lutea, resorptions and fetal evaluations. No reproductive toxicity was observed, resulting in a NOAEL of 2000 mg/kg-day (OECD, 2006; ECHA, 1992).	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (Only 1 species (rats) has been tested)
Developmental toxicity	Low	EPA assessed the potential for 1-eicosanol to induce developmental toxicity using read-across from 1-docosanol and 1-octadecanol. Rabbits exposed to 1-docosanol during GD 6-19 reported a NOAEL of 2000 mg/kg-day (OECD, 2006; Iglesias et al., 2002c). In the same OECD Guideline 422 study discussed under repeated dose and reproductive toxicity, rats were exposed to 1-octadecanol in their diet for 45 days (males) to 54 days (females) (OECD, 2006; ECHA, 1992). Fetal endpoints included litter size, litter weight, sex ratio and fetal anomalies (visceral and external). No developmental toxicity was observed, resulting in a NOAEL of 2000 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Developmental Toxicity Risk Assessment; EPA has not established the suitability of the analog data.
Neurodevel. toxicity	NA	Not rated	Data gap	EPA should clarify whether neurodevelopmental endpoints were assessed in the available experimental data.

11. 1,2-Hexanediol, CAS RN 6920-22-5

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Based on 1,2-hexanediol's metabolism, a lack of structural alerts and experimental genotoxicity studies (Section 6.1.5), 1,2-hexanediol is of low concern for carcinogenicity or mutagenicity.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	The sub-chronic toxicity study discussed in Section 6.1.3 also examined estrous cycle evaluations in females and sperm parameters (sperm count, motility and morphology) in males. No adverse effects were noted for the evaluated reproductive parameters, resulting in a NOAEL of 1000 mg/kg-day (ECHA, 2002a, b). To further assess the reproductive and developmental toxicity potential for 1,2-hexanediol, EPA evaluated two oral gavage studies for the chemical in pregnant female rats. In the first study, results from exposure during gestation days 5-19 indicated no adverse maternal or developmental effects at the highest dose tested, resulting in a NOAEL of 300 mg/kg-day (Johnson et al., 2012; ECHA, 2006). In the second study, rats exposed during gestation days 6-19 to higher doses of 1,2-hexanediol reported no developmental effects at any doses, resulting in a developmental NOAEL at the highest dose of the study, 750 mg/kg-day. However, the females exposed to 750 mg/kg-day displayed decreased absolute and relative feed consumption, leading to decreased body weight. The maternal NOAEL for this study was 500 mg/kg-day and the LOAEL was 750 mg/kg-day (ECHA, 2003a). These results taken with the low-concern criteria oral threshold of 250 mg/kg-day indicate low concern for reproductive and developmental toxicity.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment and Guidelines for Developmental Toxicity Risk Assessment. (Sub-chronic studies are not acceptable to show low hazard, and only 1 species (rats) has been tested)
Developmental toxicity	Low		Data gap	
Neurodevel. toxicity	NA	Not rated	Data gap	

12. 1-Octadecanol, CAS RN 112-92-5

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	For this chemical, there is an absence of the types of reactive structural features that are present in genotoxic carcinogens. 1-Octadecaol is not an electrophile. Further, predictions from the Virtual models for property Evaluation of chemicals within a Global Architecture (VEGA) models' indicate 1-octadecanol has a low potential to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for 1-octadecanol to induce reproductive toxicity using experimental data. In a combined repeated dose, reproductive, and developmental toxicity OECD Guideline 422 study, rats were exposed to 1-octadecanol in their diet for 45 days (males) to 54 days (females). Endpoints evaluated include mortality, clinical signs, body weight, food consumption, estrous cycles, ovary weight and histology, testes and epididymis weight and histology, pregnancy rate, gestation length, implantations, corpora lutea, resorptions and fetal evaluations. No reproductive toxicity was observed, resulting in a NOAEL of 2000 mg/kg-day (OECD, 2006; ECHA, 1992).	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species (rats) has been tested) Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[9]
Developmental toxicity	Low	In the same OECD Guideline 422 study discussed under repeated dose and reproductive toxicity, rats were exposed to 1-octadecanol in their diet for 45 days (males) to 54 days (females) (OECD, 2006; ECHA, 1992). Fetal endpoints included litter size, litter weight, sex ratio and fetal anomalies (visceral and external). No developmental toxicity was observed, resulting in a NOAEL of 2000 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by Guidelines for Developmental Toxicity Risk Assessment. (only 1 species (rats) has been tested)
Neurodevel. toxicity	NA	Not rated	Data gap	

[9] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

13. Propanol, [2-(2-butoxymethylethoxy)methylethoxy]-, CAS RN 55934-93-5

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Tripropylene glycol-n-butyl ether's metabolism, lack of structural alerts, and negative experimental genotoxicity results indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	A one-generation reproductive study in rats exposed to dipropylene glycol monobutyl ether by oral gavage reported a reproductive NOAEL of 1000 mg/kg-day (ECHA, 1994). These results indicate low concern for reproductive toxicity by exceeding the low-concern oral threshold of 250 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species (rats) has been tested)
Developmental toxicity	Low	A developmental inhalation study in rats exposed to tripropylene glycol methyl ether aerosol from gestation days (GD) 6-15 reported a no observed adverse effect concentration (NOAEC) of 8.9 mg/L (Bio-Research Laboratories LTD, 1985a). Another developmental inhalation study in rats exposed to tripropylene glycol monomethyl ether aerosol from GD 6-15 reported a NOAEC of 1 mg/L-day (129 ppm), which is above tripropylene glycol monomethyl ether's theoretical air saturation vapor concentration of 7.88 ppm (Bio-Research Laboratories LTD, 1985b). Two studies where rats were exposed from GD 6-15 and rabbits were exposed from GD 7-19 to dipropylene glycol methyl ether vapor both reported NOAECs of 0.45 mg/L (53 ppm), which is also above dipropylene glycol methyl ether's theoretical air saturation vapor concentration of 26 ppm (ECHA, 1990a, b). These results indicate low concern for developmental toxicity from vapor exposures based on no effects at air saturation.	Data gap	Insufficient experimental data to show low hazard as required by Guidelines for Developmental Toxicity Risk Assessment. EPA has not established the suitability of the analog data.
Neurodevel. toxicity	NA	Not rated	Data gap	

14. Propanedioic acid, 1,3-diethyl ester; (Diethyl Malonate, DEM), CAS RN 105-53-3

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Diethyl malonate's metabolism, lack of structural alerts, and experimental genotoxicity studies indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for diethyl malonate to induce developmental toxicity using read-across from dimethyl malonate. In the same OECD Guideline 422 study, rats were exposed to dimethyl malonate via oral gavage for 39 days for males and 51 days for females (OECD, 2005; ECHA, 2003). Reproductive parameters including fertility indices, duration of gestation, number of corpora lutea, pre and post-implantation loss, numbers of pups born and live litters, mean litter size, sex, ratio, pup viability, and pup survivability were recorded. Pups from each litter were examined for external deformities, malformations and gross pathologies. No adverse effects were noted on any of these parameters, resulting in a NOAEL of 1000 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[10]
Developmental toxicity	Low	EPA also used read-across from an analog to assess developmental toxicity from inhalation exposures. A study in rabbits exposed to vapors of the analog dimethyl glutarate from gestation day 7 to 28 reported a no observed adverse effect concentration (NOAEC) of 1.0 mg/L based on no adverse effects noted related to developmental toxicity (Munley, 2003). EPA calculated a saturation vapor concentration of 1.55 mg/L for dimethyl glutarate. While the NOAEC of 1.0 mg/L is below the low-concern criteria threshold of 2.5 mg/L, because of limited dosing in the study and because no adverse effects were observed close to the calculated saturation vapor concentration for dimethyl glutarate, EPA uses best professional scientific judgement to conclude that these results indicate low concern for developmental toxicity for diethyl malonate.	Data gap	Insufficient experimental data to show low hazard as required by Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested and EPA has not established the suitability of the analog data)
Neurodevel. toxicity	NA	Not rated	Data gap	

[10] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

15. Propanedioic acid, 1,3-dimethyl ester; (Dimethyl Malonate, DMM), CAS RN 108-59-8

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Dimethyl malonate's metabolism, lack of structural alerts, and experimental genotoxicity studies indicate that this chemical is unlikely to be carcinogenic or mutagenic**.**	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for mammalian developmental toxicity by dimethyl malonate using experimental data from the same OECD Guideline 422 study discussed in Section 6.1.3. Rats were exposed to dimethyl malonate via oral gavage for 39 days for males and 51 days for females (OECD, 2005; ECHA, 2003). Reproductive parameters including fertility indices, duration of gestation, number of corpora lutea, pre and post-implantation loss, numbers of pups born and live litters, mean litter size, sex, ratio, pup viability, and pup survivability were recorded. Pups from each litter were examined for external deformities, malformations and gross pathologies. No adverse effects were noted on any of these parameters, resulting in a NOAEL of 1000 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. Further, OECD Guideline 422 states: "Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/ developmental effects."[11]
Developmental toxicity	Low	EPA also used read-across from an analog to assess developmental toxicity from inhalation exposures. A study in rabbits exposed to vapors of the analog dimethyl glutarate from gestation day 7 to 28 reported a no observed adverse effect concentration (NOAEC) of 1.0 mg/L based on no adverse effects related to developmental toxicity (Munley, 2003). EPA calculated a saturation vapor concentration of 1.55 mg/L for dimethyl glutarate. While the NOAEC of 1.0 mg/L is below the low- concern criteria threshold of 2.5 mg/L because of limited dosing in the study and because no adverse effects were observed close to the calculated saturation vapor concentration for dimethyl glutarate, EPA used best professional scientific judgement to conclude that these results indicate low concern for developmental toxicity for dimethyl malonate.	Data gap	Insufficient experimental data to show low hazard as required by Guidelines for Developmental Toxicity Risk Assessment. (only 1 species tested and EPA has not established the suitability of the analog data)
Neurodevel. toxicity	NA	Not rated	Data gap	

[11] OECD (2016) Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Pg. 2. https://www.oecd-ilibrary.org/environment/test-no-422-combined-repeated-dose-toxicity-study-with-the-reproduction-developmental-toxicity-screening-test_9789264264403-en

16. Propanol, 1(or 2)-(2-methoxymethylethoxy)-, acetate; (DPMA), CAS RN 88917-22-0

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	DPMA's metabolism and excretion, lack of structural alerts, and experimental genotoxicity studies indicate that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	A one-generation reproductive study in rats exposed to dipropylene glycol monobutyl ether by oral gavage reported a reproductive NOAEL of 1000 mg/kg-day (ECHA, 1994). These results indicate low concern for reproductive toxicity by exceeding the low-concern threshold of 250 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species tested)
Developmental toxicity	Low	A developmental inhalation study in rats exposed to tripropylene glycol methyl ether aerosol from gestation days (GD) 6-15 reported a NOAEC of 8.9 mg/L (Bio-Research Laboratories LTD, 1985a). Another developmental inhalation study in rats exposed to tripropylene glycol monomethyl ether aerosol from GD 6-15 reported a NOAEC of 1 mg/L-day (129 ppm) (Bio-Research Laboratories LTD, 1985b). Two studies where rats were exposed from GD 6-15 and rabbits were exposed from GD 7-19 to dipropylene glycol methyl ether vapor both reported NOAECs of 0.45 mg/L (53 ppm), which is above dipropylene glycol methyl ether's theoretical air saturation vapor concentration of 26 ppm (ECHA, 1990a, b). These results indicate low concern for developmental toxicity from vapor exposures based on no effects at air saturation and from aerosols by exceeding the low-concern threshold of 0.5 mg/L for aerosol inhalation exposures.	Data gap	Insufficient experimental data to show low hazard as required by Guidelines for Developmental Toxicity Risk Assessment. (EPA has not established the suitability of the analog data)
Neurodevel. toxicity	NA	Not rated	Data gap	

17. Propanol, [(1-methyl-1,2-ethanediyl)bis(oxy)]bis-; (Tripropylene glycol), CAS RN 24800-44-0

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	EPA assessed the potential for tripropylene glycol to cause carcinogenicity in mice and rats using read across from dipropylene glycol. A study on rats exposed to dipropylene glycol in drinking water for two years demonstrated no dose-related effects on cancer incidence or cancer-related effects at the highest dose tested (3040 mg/kg-day in males, 2330 mg/kg-day in females), resulting in a negative finding for carcinogenicity (ECHA, 2004a, b; NTP, 2004). Similarly, a study on mice exposed to dipropylene glycol in drinking water for two years also demonstrated no adverse effects at the highest dose tested (2390 mg/kg-day in males, 1950 mg/kg-day in females), resulting in a negative finding for carcinogenicity (ECHA, 2004a; NTP, 2004).	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment. (EPA has not established the suitability of the analog)
Reproductive toxicity	Low	EPA assessed the potential for mammalian reproductive and developmental toxicity using the combined repeated dose, reproductive, and developmental study discussed in Section 6.1.3 (OECD, 1994; ECHA, 1993c). Rats were exposed to tripropylene glycol via gavage for 49 days, beginning 14 days prior to mating and continuing through lactation day 3 for females. The authors reported no reproductive (mating, fertility and estrus cycle) or developmental effects (external examinations of the pups and pup body weight gain) at the highest dose tested (1000 mg/kg-day). The NOAEL for this study was 1000 mg/kg-day.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species tested)
Developmental toxicity	Low	EPA further assessed the potential for developmental toxicity using read across from dipropylene glycol. A study on pregnant rats exposed during gestational day (GD) 6-15 reported a developmental NOAEL of 2000 mg/kg-day and a LOAEL of 5000 mg/kg-day based on decreased fetal weight (OECD, 2001; BUA, 1996; Bates et al., 1992b; ECHA, 1990b). A study on rabbits exposed to dipropylene glycol during GD 6-19 reported no adverse effects at the highest dose tested (1200 mg/kg-day), resulting in a NOAEL of 1200 mg/kg-day (OECD, 2001; Bates et al., 1992a; ECHA, 1990a).	Data gap	Insufficient experimental data to show low hazard as required by Guidelines for Developmental Toxicity Risk Assessment. (EPA has not established the suitability of the analog)
Neurodevel. toxicity	NA	Not rated	Data gap	

18. 2-Propanol, 1,1'-oxybis- (1,1’-Dimethyldiethylene Glycol), CAS RN 110-98-5

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	EPA assessed the potential for 1,1’-dimethyldiethylene glycol to cause carcinogenicity in mice and rats using read-across from dipropylene glycol. Rats exposed to dipropylene glycol in drinking water for 2 years demonstrated no dose-related effects on cancer incidence or cancer-related effects at the highest dose tested (3040 mg/kg-day in males, 2330 mg/kg-day in females), resulting in a negative finding for carcinogenicity (ECHA, 2004b; NTP, 2004). Similarly, mice exposed to dipropylene glycol in drinking water for two years also demonstrated no adverse effects at the highest dose tested (2390 mg/kg-day in males, 1950 mg/kg-day in females), resulting in a negative finding for carcinogenicity (ECHA, 2004a; NTP, 2004).	Data gap	Insufficient experimental data to show low hazard as required by EPA’s Guidelines for Carcinogen Risk Assessment. (EPA has not established the suitability of the analog)
Reproductive toxicity	Low	EPA assessed the potential for reproductive toxicity using read-across from analog tripropylene glycol. In a combined repeated dose, reproductive, and developmental study, rats were exposed to tripropylene glycol via oral gavage for 49 days, beginning 14 days prior to mating and continuing through lactation day 3 for females. The authors reported no reproductive (mating, fertility, and estrus cycle) or developmental effects (external examinations of the pups and pup body weight gain) at the highest dose tested (1000 mg/kg-day). EPA determined the NOAEL for this study was 1000 mg/kg-day (OECD, 1994).	Data gap	Insufficient experimental data to show low hazard as required by EPA’s Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species tested)
Developmental toxicity	Low	EPA further assessed the potential for developmental toxicity, using read-across from an analog, dipropylene glycol. A study on pregnant rats orally exposed to dipropylene glycol during GD 6-15 reported a developmental NOAEL of 2000 mg/kg-day and a LOAEL of 5000 mg/kg-day based on decreased fetal weight. A study on rabbits orally exposed to dipropylene glycol during GD 6-19 reported no adverse effects at the highest dose tested, resulting in a NOAEL of 1200 mg/kg-day (OECD, 2001; Bates et al., 1992a; ECHA, 1990a).	Data gap	Insufficient experimental data to show low hazard as required by Guidelines for Developmental Toxicity Risk Assessment. (EPA has not established the suitability of the analog)
Neurodevel. toxicity	NA	Not rated	Data gap	

19. Propanol, oxybis-; (Oxydipropanol; Dipropylene glycol), CAS RN 25265-71-8

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	EPA assessed the potential for dipropylene glycol to cause carcinogenicity in mice and rats. Rats exposed to dipropylene glycol in drinking water for 2 years demonstrated no dose-related increase in cancer incidence and no cancer-related effects at the highest dose tested (3040 mg/kg-day in males, 2330 mg/kg-day in females), resulting in a negative finding for carcinogenicity (ECHA, 2004a, b; NTP, 2004). Similarly, mice exposed to dipropylene glycol in drinking water for two years also found no adverse effects at the highest dose tested (2390 mg/kg-day in males, 1950 mg/kg-day in females), resulting in a negative finding for carcinogenicity (ECHA, 2004a; NTP, 2004).	Low	Sufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment, provided the studies referenced are high quality when evaluated by a validated systematic review method.
Reproductive toxicity	Low	EPA assessed the potential for reproductive toxicity using read-across from an analog, tripropylene glycol. In a combined repeated dose, reproductive, and developmental study, rats were exposed to tripropylene glycol via oral gavage for 49 days, beginning 14 days prior to mating and through lactation day 3 for females. The authors reported no reproductive (mating, fertility, and estrus cycle) or developmental effects (external examinations of the pups and pup body weight gain) at the highest dose tested (1000 mg/kg-day). The NOAEL for this study was 1000 mg/kg-day (OECD, 1994; ECHA, 1993b).	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment. (only 1 species tested)
Developmental toxicity	Low	To further assess the potential for developmental toxicity, EPA evaluated two oral gavage studies on dipropylene glycol. A study on pregnant rats exposed during gestational day (GD) 6-15 reported a developmental NOAEL of 2000 mg/kg-day and a LOAEL of 5000 mg/kg-day based on decreased fetal weight (OECD, 2001; BUA, 1996; Bates et al., 1992b; ECHA, 1990b). A study on rabbits exposed to dipropylene glycol during GD 6-19 reported no adverse effects at the highest dose tested (1200 mg/kg-day), resulting in a NOAEL of 1200 mg/kg-day (OECD, 2001; Bates et al., 1992a; ECHA, 1990a).	Low	Sufficient experimental data to show hazard as required by Guidelines for Developmental Toxicity Risk Assessment, provided the studies referenced are high quality when evaluated by a validated systematic review method.
Neurodevel. toxicity	NA	Not rated	Data gap	

20. Tetracosane, 2,6,10,15,19,23-hexamethyl- ; (Squalane), CAS RN 111-01-3

Endpoint	EPA hazard rating	EPA basis	Recommended rating	Recommendation basis
Carcinogenicity	Low	Squalane's limited absorption, metabolism, a lack of structural alerts, and experimental genotoxicity studies indicates that this chemical is unlikely to be carcinogenic or mutagenic.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Carcinogen Risk Assessment.
Reproductive toxicity	Low	EPA assessed the potential for reproductive and developmental toxicity using the same combined repeated dose, reproductive, and developmental study discussed above. Rats were exposed to squalane by oral gavage for 28 days. (ECHA, 2013e). Males were treated two weeks prior to mating and females were treated two weeks prior to mating through postpartum day 4. No reproductive (mating, fertility, and estrus cycle) or developmental effects (external examinations of the pups and pup body weight gain) at the highest dose tested (1000 mg/kg-day) were observed. The NOAEL for this study was 1000 mg/kg-day for both reproductive and developmental toxicity.	Data gap	Insufficient experimental data to show low hazard as required by EPA's Guidelines for Reproductive Toxicity Risk Assessment and Guidelines for Developmental Toxicity Risk Assessment. (Sub-chronic studies are not acceptable to show low hazard, and only 1 species (rats) has been tested)
Developmental toxicity	Low		Data gap	
Neurodevel. toxicity	NA	Not rated	Data gap	