UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments of Safer Chemicals Healthy Families,

Natural Resources Defense Council,

Earthjustice, and

Environmental Health Strategy Center

on Proposed Low-Priority Substance Designation Under Section 6(b)(1) of the Toxic Substances Control Act (TSCA)

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Docket Numbers:

EPA-HQ-OPPT-2019-0106,EPA-HQ-OPPT-2019-0107,EPA-HQ-OPPT-2019-0108, EPA-HQ-OPPT-2019-0109, EPA-HQ-OPPT-2019-0110, EPA-HQ-OPPT-2019-0111, EPA-HQ-OPPT-2019-0112, EPA-HQ-OPPT-2019-0113, EPA-HQ-OPPT-2019-0114, EPA-HQ-OPPT-2019-0115, EPA-HQ-OPPT-2019-0116, EPA-HQ-OPPT-2019-0117, EPA-HQ-OPPT-2019-0118, EPA-HQ-OPPT-2019-0119, EPA-HQ-OPPT-2019-0120, EPA-HQ-OPPT-2019-0121, EPA-HQ-OPPT-2019-0122, EPA-HQ-OPPT-2019-0123, EPA-HQ-OPPT-2019-0124, EPA-HQ-OPPT-2019-0125, EPA-HQ-OPPT-2019-0450

Safer Chemicals Healthy Families (SCHF), Natural Resources Defense Council (NRDC), Earthjustice, and Environmental Health Strategy Center submit these comments on the August 15, 2019 proposal of the Environmental Protection Agency (EPA) to designate 20 chemicals for low-priority listing under section 6(b)(1) of the Toxic Substances Control Act (TSCA).[1] Our organizations are committed to assuring the safety of chemicals used in our homes, workplaces, and the many products to which our families and children are exposed each day. They took a leadership role during the TSCA legislative process, advocating the most protective and effective legislation possible to reduce the risks of toxic chemicals in use today.

EXECUTIVE SUMMARY

The prioritization process in section 6(b)(1) of TSCA is the primary tool in the law for selecting chemicals that will be evaluated to determine whether they present unreasonable risks of injury to human health and the environment. Chemicals found to present unreasonable risks in these evaluations must be banned or otherwise restricted under section 6(a) to the extent necessary to eliminate these risks. Section 6(b)(2)(B) of TSCA requires EPA to designate at least 20 high-priority and 20 low-priority substances within 3.5 years of enactment of the 2016 TSCA amendments. High-priority chemicals are defined as those that "may present an unreasonable risk" because of "a potential hazard and a potential route of exposure." EPA must immediately initiate risk evaluations on substances listed as high-priority. Substances designated as low-

[1] 84 Federal Register 41712.

priority are those for which EPA has information sufficient to establish that they do "not meet the standard. . . for . . . a high-priority substance" – *i.e.* do not present an unreasonable risk of injury because they lack a potential hazard or a potential route of exposure. Substances listed as low-priority are deemed not to warrant TSCA risk evaluations.

EPA has proposed the following twenty chemicals for low-priority listing:

Chemical name	**CAS RN**	**Docket**
#1- 1-Butanol, 3-methoxy-, 1-acetate	4435-53-4	EPA-HQ-OPPT-2019-0106
#2- D-gluco-Heptonic acid, sodium salt (1:1), (2.xi.)-	31138-65-5	EPA-HQ-OPPT-2019-0107
#3- D-Gluconic acid	526-95-4	EPA-HQ-OPPT-2019-0108
#4- D-Gluconic acid, calcium salt (2:1)	299-28-5	EPA-HQ-OPPT-2019-0109
#5- D-Gluconic acid, .delta.-lactone; (Gluconolactone)	90-80-2	EPA-HQ-OPPT-2019-0110
#6- D-Gluconic acid, potassium salt (1:1)	299-27-4	EPA-HQ-OPPT-2019-0111
#7- D-Gluconic acid, sodium salt (1:1)	527-07-1	EPA-HQ-OPPT-2019-0112
#8- Decanedioic acid, 1,10-dibutyl ester	109-43-3	EPA-HQ-OPPT-2019-0113
#9- 1-Docosanol	661-19-8	EPA-HQ-OPPT-2019-0114
#10- 1-Eicosanol	629-96-9	EPA-HQ-OPPT-2019-0115
#11- 1,2-Hexanediol	6920-22-5	EPA-HQ-OPPT-2019-0116
#12- 1-Octadecanol	112-92-5	EPA-HQ-OPPT-2019-0117
#13- Propanol, [2-(2-butoxymethylethoxy)methylethoxy]-	55934-93-5	EPA-HQ-OPPT-2019-0118
#14- Propanedioic acid, 1,3-diethyl ester; (Dimethyl Malonate, DMM)	105-53-3	EPA-HQ-OPPT-2019-0119
#15- Propanedioic acid, 1,3-dimethyl ester; (Diethyl Malonate, DEM)	108-59-8	EPA-HQ-OPPT-2019-0120
#16- Propanol, 1(or 2)-(2-methoxymethylethoxy)-, acetate; (DPMA)	88917-22-0	EPA-HQ-OPPT-2019-0121
#17- Propanol, [(1-methyl-1,2-ethanediyl)bis(oxy)]bis-; (Tripropylene glycol)	24800-44-0	EPA-HQ-OPPT-2019-0122
#18- 2-Propanol, 1,1'-oxybis-; (Dipropylene glycol #1)	110-98-5	EPA-HQ-OPPT-2019-0123

#19- Propanol, oxybis-; (Oxydipropanol; Dipropylene glycol)	25265-71-8	EPA-HQ-OPPT-2019-0124
#20- Tetracosane, 2,6,10,15,19,23-hexamethyl- ; (Squalane)	111-01-3	EPA-HQ-OPPT-2019-0125

Many of these chemicals are produced in large volumes and are present in a range of products to which pregnant women, children, and other consumers and workers are exposed. Listing these chemicals as low-priority will remove them from the risk evaluation process under TSCA and signify to industry and the public that they lack the potential to harm health or the environment. As a result, production, use, and exposure could increase without any regulatory scrutiny. However, EPA's proposal does not contain sufficient data to establish that the 20 chemicals lack unreasonable risks to health or the environment, including to potentially exposed and susceptible subpopulations, and its prioritization methodology systematically ignores or understates evidence that raises concern about those chemicals' adverse effects.

Our comments focus on a series of overarching flaws with EPA's proposed low-priority chemical designations. We document these flaws with numerous chemical-specific examples drawn from the EPA dossiers that purport to document the scientific basis for low-priority listing. In light of the flaws we demonstrate, EPA has failed to justify low-priority listings for all of the 20 chemicals, and they must therefore be designated high-priority under TSCA.

As we show in our comments, TSCA requires EPA to justify low-priority listings with evidence establishing the absence of any potential for unreasonable risk. However, EPA has failed to meet these requirements for low-priority designation for all 20 chemicals. The deficiencies in EPA's proposal are extensive and fall into the following categories:

- *EPA's dossiers for the 20 chemicals contain fundamental gaps in the health effects data necessary to establish that the chemicals lack potential hazards*
    - EPA fails to consider immunotoxicity, endocrine and neurodevelopmental health endpoints for all 20 proposed low-priority chemicals
    - The proposed low-priority listings are based on screening data that are insufficient under EPA's risk assessment guidelines to determine that a substance lacks reproductive and developmental effects
    - EPA's determinations that the 20 chemicals are non-mutagenic are not based on a sufficient battery of in vivo and in vitro assays to demonstrate the absence of mutagenic activity
    - EPA's low-priority dossiers fail to provide sufficient data to classify a substance as non-carcinogenic under EPA risk assessment guidelines
    - Although respiratory sensitization is a required element of EPA's hazard classification system, data on this endpoint are lacking in several dossiers
    - EPA lacks acute inhalation data for some of the 20 chemicals and thus has no basis for a low-hazard determination for inhalation exposure
- *EPA's low hazard determinations suffer from numerous deficiencies in methodology, disregard relevant data and misclassify the studies on which EPA relies*

- EPA has not transparently documented the quality and reliability of the data it is relying on for the 20 low-priority candidates
- Despite relying heavily on data on analogs, EPA has not adequately shown that these analogs are strong surrogates for low-priority candidates
- EPA over-relies on highly uncertain modeling predictions in the absence of data on the low-priority candidate or an analog and repeatedly misinterprets its modeling results
- EPA's hazard classification system incorporates a high-dose threshold for reproductive and developmental effects, but GHS and other classification systems do not include this approach and EPA has failed to justify it
- EPA misapplies the GHS criteria for acute toxicity, resulting in significantly lower hazard thresholds than GHS requires
- EPA uses undefined and unquantified descriptors to dismiss hazard and exposure concerns
- EPA dismisses data that should be considered evidence of hazard under its hazard classification criteria and wrongly relies on studies that in fact show evidence of adverse effects

- *EPA fails to address the increased exposure and susceptibility of vulnerable populations in its low hazard determinations, relying instead on boilerplate language that dismisses these heightened risks without any underlying analysis*

- *EPA fails to adequately assess the low priority chemicals' environmental hazards*

  - EPA's classification system for environmental hazard is incomplete, arbitrary and contrary to other established systems
  - EPA evaluates an inadequate range of ecological endpoints

While these deficiencies affect all of the low-priority candidates, they are particularly stark for two chemicals -- 3-Methoxybutyl Acetate and Dibutyl Sebacate. To underscore the many reasons why these chemicals do not warrant low-priority listing under TSCA, Parts III and IV of these comments draw together our multiple concerns about EPA's proposal to designate them as low-priority.

I. EPA MUST JUSTIFY LOW-PRIORITY LISTINGS WITH EVIDENCE ESTABLISHING THE ABSENCE OF ANY POTENTIAL FOR UNREASONABLE RISK

Section 6(b)(1)(B)(ii) authorizes a substance to be listed as low-priority –

> "if the Administrator concludes, based on information sufficient to establish, . . . that such substance does not meet the standard identified in clause (i) for designating a chemical substance a high-priority substance."

The prerequisite for high-priority listing under section 6(b)(1)(B)(i) is a determination that a chemical "may present an unreasonable risk" because of "a potential hazard and a potential route of exposure." 15 U.S.C. § 2605(b)(1)(B)(i). Thus, a chemical will qualify as low priority only if it can be demonstrated to *lack any potential for unreasonable risk because of the absence of a potential hazard or a potential exposure. Id.* § 2605(b)(1)(B)(ii).

Neither the high-priority nor the low-priority definitions in TSCA require a determination of whether a chemical is or is not expected to cause adverse effects at the levels of exposure anticipated under its

conditions of use. This is the function of a risk evaluation, which is not part of the prioritization process. Thus, EPA's proposed high-priority listings merely identify the adverse health and environmental effects reported in the literature for various health and environmental endpoints and provide evidence of potential exposure.[2] Correspondingly, to designate a chemical as low priority, EPA must establish the *absence of adverse effects or potential exposure*. Where there is potential exposure, EPA cannot justify a low-priority designation for chemicals that present potential hazards because it believes there is a small likelihood of harm under their conditions of use. This would amount to a "no risk" determination, which Congress clearly excluded from prioritization under section 6(b)(1) and created a separate process for that under section 6(b)(4).

As with high-priority listings, a low-priority listing must reflect the circumstances of "potentially exposed or susceptible populations" as well as the general population. *Id.* Thus, EPA must show that the chemical does not pose an unreasonable risk to these subpopulations because of the absence of either potential hazard or a potential route by which they may be exposed.

The absence of potential hazard or a route of exposure cannot be assumed merely because hazard or exposure data are unavailable. EPA must instead have "information sufficient to establish" that the chemical is without the potential for unreasonable risk. *Id.* This will require that the Agency identify data demonstrating the absence of potential hazard for all relevant toxicological endpoints. The data relied on by EPA must be of sufficient quality, scope and reliability to "establish" that the chemical is not hazardous. Data that are incomplete, preliminary or equivocal will not satisfy this standard because they will be insufficient to rule out unreasonable risk.

Where EPA lacks sufficient data to make a low-priority determination, TSCA requires EPA to acquire the data. Section 26(k) of TSCA directs EPA to consider "reasonably available" information when making prioritization decisions, 15 U.S.C. § 2625(k), and EPA's prioritization rule defines "reasonably available information" as "information that EPA possesses *or can reasonably generate, obtain and synthesize* for use, considering the deadlines specified in 15 U.S.C. 2605(b) for prioritization and risk evaluation." 40 C.F.R. § 702.3 (emphasis added). In the preamble to that rule, EPA wrote that "it makes sense to view information that can be obtained through testing as 'reasonably available' in some instances—especially information that can be generated through short-term testing, where it can be obtained within the relevant statutory deadlines and the information would be of sufficient value to merit the testing." 82 Fed. Reg. 33757 (July 20, 2017). Given that EPA has had three and a half years from the enactment of the 2016 TSCA Amendments to designate 20 low priority chemicals, test data that could have been required and developed during that period should be considered "reasonably available" under the statutory definition.

Section 6(b)(1)(C)(iii) provides that, where EPA has proposed a chemical for low-priority listing but determines that the available data are insufficient to support listing, the chemical must be listed as high-priority. *Id.* § 2605(b)(1)(C)(iii). *See also* 40 CFR § 702.7(e). This confirms that unless EPA can conclusively establish the absence of unreasonable risk, the chemical will be deemed to meet the high-priority definition and therefore will require a full risk evaluation.

[2] See, e.g., Proposed Designation of 1,3-Butadiene (CASRN 106-99-0) as a High-Priority Substance for Risk Evaluation at 29; Proposed Designation of Formaldehyde (CASRN 50-00-0) as High-Priority Substance for Risk Evaluation at 60-63.

II. EPA HAS FAILED TO PROVIDE INFORMATION ESTABLISHING THAT THE LOW-PRIORITY CANDIDATES SATISFY THE STATUTORY REQUIREMENTS FOR LOW-PRIORITY DESIGNATION

EPA has based the 20 proposed low-priority listings primarily on EPA's findings of "low" potential hazard to human health and the environment. The background dossiers for the 20 chemicals generally discuss their uses, production volumes, exposures and vulnerable populations, but this information scarcely factors into EPA's application of the low-priority criteria. For instance, EPA does not calculate expected exposure levels under any of the 20 chemicals' conditions of use. Instead, the Agency's determinations that the 20 chemicals lack potential hazards is based largely on a table entitled *Low-Concern Criteria for Human Health and Environmental Fate and Effects*, which is included in each of the chemical-specific dossiers. The health endpoints encompassed by the table are acute toxicity, repeated-dose toxicity, reproductive effects, developmental effects, mutagenicity/genotoxicity, carcinogenicity, neurotoxicity, sensitization, and irritation/corrosivity. For these endpoints, the table includes criteria for categorizing hazard as High (or Very High), Moderate or Low. The table also addresses acute and chronic aquatic toxicity, persistence, and potential for bioaccumulation and provides criteria for determining "low concern" for environmental hazard. Where toxicity is rated Low for all health and environmental endpoints, EPA concludes that the chemical meets the TSCA definition of low priority. For certain chemicals, discussed below, EPA has also proposed low-priority designations despite finding "moderate" hazard for some endpoints, without adequate explanation of why such hazards could not pose unreasonable risk.

As shown below, there are several fundamental flaws both in EPA's Low-Concern Criteria and how EPA has applied these criteria to the 20 low-priority candidates. EPA's criteria do not include all the endpoints that are necessary to support a low-priority designation and EPA frequently relies on data that are not adequate for definitive "no hazard" findings. In addition, the EPA hazard criteria themselves are in several cases unprotective and lacking in justification. EPA also seeks to compensate for the lack of data with excessive reliance on analogs and predictive models that are inadequate to demonstrate the absence of potential hazards, and in many cases, it ignores evidence that a low-priority candidate in fact has adverse effects. Finally, EPA overlooks significant quality issues with some studies and erroneously characterizes the conclusions of others. Because of these many flaws, the dossiers fail to meet EPA's burden of presenting "information sufficient to establish" the absence of potential hazard and thus the absence of unreasonable risk. As a result, listing the 20 chemicals as low-priority under TSCA is unwarranted.

The absence of high-quality, reliable data for all relevant endpoints for the low-priority candidates could have been avoided if, as our groups have repeatedly urged, EPA had months (or even years) ago conducted a careful analysis of data sufficiency for these chemicals. This analysis would have enabled EPA to identify data gaps that needed to be filled before EPA could establish the lack of potential hazard to health and the environment required for low-priority listing under TSCA. EPA could then have issued test rules or orders under TSCA section 4 requiring manufacturers to conduct testing to develop this information. Instead, EPA has chosen to rely for its proposal on an incomplete and weak database rife with gaps and uncertainties that now preclude low-priority listing under the law.

The many flaws in the dossiers on the 20 low-priority candidates can be grouped into several categories, which are discussed in detail below.

A. EPA's Dossiers Contain Fundamental Gaps in the Health Effects Data Necessary to Establish That Chemicals Meet the Low Priority Definition

1. EPA Fails to Consider Immunotoxicity, Endocrine, and Neurodevelopmental Health Endpoints for All 20 Proposed Low-Priority Chemicals

For all 20 proposed low-priority chemicals, EPA fails to consider relevant health endpoints, including immunotoxicity, endocrine effects, and developmental neurotoxicity. In the absence of information about those endpoints, EPA cannot finalize any of its low-priority designations.

Immunotoxicity. As noted above, EPA may only designate a chemical as low-priority if EPA has "information sufficient to establish … that such substance does not meet the standard" for high-priority designation. 15 U.S.C. § 2605(b)(1)(B)(ii). EPA's risk evaluation rule specifically mentions immune system effects as a relevant hazard to be considered in TSCA risk evaluations. 82 Fed. Reg. 33742.[3] In evaluating chemicals for high-priority designation, EPA expressly considers immunotoxicity, and it has cited immune system effects in support of several of its proposed high-priority listings.[4] Similarly, EPA has considered immune system effects in several of the draft risk evaluations it has released under TSCA. *See, e.g.*, Draft Risk Evaluation for Methylene Chloride at 234-37, 260-61; Draft Risk Evaluation for HBCD at 301, 307-08. EPA's risk evaluation rule specifically mentions immune system effects as a relevant hazard to be considered in TSCA risk evaluations. 82 Fed. Reg. 33742. EPA has thus repeatedly acknowledged that immunotoxicity is one of the hazard endpoints that must be considered when prioritizing chemicals and conducting risk evaluations.

Immunotoxicity is particularly relevant to vulnerable populations since it is linked to chronic debilitating autoimmune diseases like Rheumatoid arthritis, Lupus, and Hashimoto's thyroid disease. Autoimmune diseases affect 23.5 million Americans, of which about 80 percent are women.[5] While doctors and scientists don't fully understand why women are more vulnerable, it is well-established that they are, and toxic chemical exposures are thought to be a contributing factor.[6] EPA cannot ignore this important health endpoint, particularly for vulnerable populations including women.

In its proposed low-priority chemical designations, however, EPA does not cite a single immunotoxicity study or discuss any of the chemicals' immune system effects. Without such consideration, EPA is ignoring an endpoint that is directly relevant to low-priority listing. Since EPA would rely on evidence of immunotoxicity to determine that a high-priority candidate "may present an unreasonable risk of injury to health or the environment," it must be able to demonstrate the absence of immunotoxicity in determining that a low-priority candidate lacks the potential for unreasonable risk. 15 U.S.C. §

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[3] *See also National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press* at 204 (referring to immunotoxicity as an "end point of great concern" for risk evaluation); 40 CFR § 158.500 (identifying immunotoxicity as a "toxicology data requirement" for EPA's review of pesticides).

[4] *See, e.g.,* Proposed Designation of 1, 2-Dichloroethane (CASRN 107-06-2) as a High-Priority Substance at 22, 29; Proposed Designation of 1,3-Butadiene (CASRN 106-99-0) as a High-Priority Substance for Risk Evaluation at 30, 36.

[5] See Johns Hopkins Medicine, "Autoimmune Disease: Why is My Immune System Attacking Itself?" Available at https://www.hopkinsmedicine.org/health/wellness-and-prevention/autoimmune-disease-why-is-my-immune-system-attacking-itself

[6] Pollard KM, Hultman P, Kono DH. Toxicology of autoimmune diseases. Chem Res Toxicol. 2010;23(3):455–466. doi:10.1021/tx9003787

2605(b)(1)(B)(i). EPA's failure to consider the 20 chemicals' potential immune system effects thus violates TSCA.

Endocrine Effects. EPA also fails to consider the low-priority candidates' potential endocrine effects. EPA has issued endocrine disruptor test guidelines that are intended "to inform regulatory decisions under TSCA …"[7] EPA has also identified endocrine activity as a relevant endpoint for analysis under its Safer Choice program, which provides criteria for identifying chemicals that warrant the Safer Choice Label.[8]

ECHA's guidance for the identification of endocrine disruptors describes the studies required to support the absence of adverse effects on estrogenic, androgenic, thyroidal and steroidogenic modalities (EATS).[9] 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)[10] or a two-generation reproductive toxicity study (OECD TG 416; test protocol according to latest version of January 2001)[11]

- 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. If there is evidence that a chemical interferes with hormone production and activity under its conditions of use, those effects would justify a high-priority designation and a TSCA risk evaluation. The absence of endocrine activity should thus be a prerequisite for low-priority listing.

In its proposed low-priority designations, however, EPA does not once discuss any of the chemicals' endocrine effects. EPA's disregard of this endpoint violates its obligation to consider all potential hazards relevant to a determination of potential unreasonable risk in applying the TSCA definition of low-priority substance.

Neurodevelopmental Toxicity. In its draft risk evaluations, EPA has acknowledged that neurodevelopmental toxicity is a relevant health endpoint that may support a determination of unreasonable risk. *See, e.g.,* Draft HBCD Risk Evaluation at 306-307; Draft NMP Risk Evaluation at 172

[7] *See, e.g.,* Final Test Guidelines; Endocrine Disruptor Screening Program Test Guidelines (Series 890); Three Tier 2 Non-Mammalian Tests, 80 Fed. Reg. 51,558 (Aug. 25, 2015).
[8] Office of Pollution Prevention & Toxics, *EPA's Safer Choice Program Master Criteria for Safer Ingredients*, Version 2.1 September 2012, available at https://www.epa.gov/sites/production/files/2013-12/documents/dfe_master_criteria_safer_ingredients_v2_1.pdf
[9] 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
[10] 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
[11] 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

("Developmental neurotoxicity endpoints have also been evaluated.").[12] Therefore, EPA must consider neurodevelopmental effects in determining whether any of the low-priority chemicals present the potential for unreasonable risk.

In collaboration with Health Canada, EPA has published an updated Developmental Neurotoxicity (DNT) guidance document on "the review and interpretation of submitted DNT data to provide guidance on how to evaluate the quality, the conduct, and resulting data derived from the behavioral methods employed in the OECD and/or EPA DNT Guidelines."[13] 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. However, while data on neurodevelopmental toxicity is necessary to establish that a low-priority candidate has no potential for unreasonable risk, EPA lacks data on neurodevelopmental toxicity for all of the proposed low-priority chemicals.

2. The Proposed Low-Priority Listings Are Based on Screening Data That Are Insufficient Under EPA's Risk Assessment Guidelines to Determine That a Substance Lacks Reproductive and Developmental Effects

The 1991 EPA Guidelines for Developmental Toxicity Risk Assessment set a high standard for the evidence required to conclude that a substance lacks adverse developmental effects:

> "More evidence is necessary to judge that an agent is unlikely to pose a hazard for developmental toxicity than that required to judge a potential hazard. This is because it is more difficult, both biologically and statistically, to support a finding of no apparent adverse effect than a finding of an adverse effect. For example, to judge that a hazard for developmental toxicity could exist for a given agent, the minimum evidence necessary would be data from a single, appropriate, well-executed study in a single experimental animal species that demonstrate developmental toxicity, and/or suggestive evidence from adequately conducted clinical/epidemiologic studies. On the other hand … when no data are available on developmental toxicity, as well as for databases from studies in animals or humans that have a limited study design (e.g., small numbers, inappropriate dose selection/exposure information, other uncontrolled factors), or data from a single species reported to have no adverse developmental effects, or databases limited to information on structure/activity relationships, short-term tests, pharmacokinetics, or metabolic precursors."[14]

According to the guidelines, "to judge that an agent is unlikely to pose a hazard for developmental toxicity, the minimum evidence would include data from appropriate, well-executed laboratory animal studies in several species (at least two) which evaluated a variety of the potential manifestations of

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[12] *See also National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press* at 204 (referring to developmental neurotoxicity as an "end point of great concern" for risk evaluation); 40 CFR § 158.500 (identifying developmental neurotoxicity as a "toxicology data requirement" for EPA's review of pesticides).

[13] 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

[14] EPA 1991. Guidelines for Developmental Toxicity Risk Assessment. Pages 40-41. Available at https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf

developmental toxicity and showed no adverse developmental effects at doses that were minimally toxic to the adult animal."

The Guidelines also provide that short-term tests in general are insufficient for assessing developmental risks, stating that

> "The need for short-term tests for developmental toxicity has arisen from the need to establish testing priorities for the large number of agents in or entering the environment, the interest in reducing the number of animals used for routine testing, and the expense of testing. These approaches may be useful in making preliminary evaluations of potential developmental toxicity, for evaluating structure-activity relationships, and for assigning priorities for further, more extensive testing… *However, the Agency currently considers a short-term test as "insufficient" by itself to carry out a risk assessment*" (emphasis added) p. 19.

The wisdom of this Guidance was recently confirmed in a 2017 report of the National Academies, *Using 21st Century Science to Improve Risk-Related Evaluations*, which concluded that emerging alternative non-animal toxicity tests are limited, as they show an incomplete picture of biology. For example, there is no cellular test that can model how a chemical may affect the ability of a child to pay attention and learn well.

The 1996 EPA Guidelines for Reproductive Toxicity Risk Assessment likewise emphasize the limitations of screening studies.[15] For example, the Guidelines highlight (p.7) the importance of an adequate duration of dosing:

> "To evaluate adequately the potential effects of an agent on the reproductive systems, a prolonged treatment period is needed. For example, damage to spermatogonial stem cells will not appear in samples from the cauda epididymis or in ejaculates for 8 to 14 weeks, depending on the test species. With some chemical agents that bioaccumulate, the full impact on a given cell type could be further delayed, as could the impact on functional endpoints such as fertility. In such situations, adequacy of the dosing duration is a critical factor in the risk assessment."

Commenting on screening studies, the Guidelines advise (p.12) that "[t]heir limited exposure periods do not allow assessment of certain aspects of the reproductive process, such as developmentally induced effects on the reproductive systems of offspring."

The Guidelines also underscore (p.10) EPA's position that "a comprehensive reproductive risk assessment should include results from a two-generation test or its equivalent" and explain that:

> "[A] one-generation study is insufficient to identify all potential reproductive toxicants, because it would exclude detection of effects caused by prenatal and postnatal exposures (including the prepubertal period) as well as effects on germ cells that could be transmitted to and expressed in the next generation. For example, adverse transgenerational effects on reproductive system development by agents that disrupt endocrine control of sexual differentiation would be missed. A one-generation test might also miss adverse effects with delayed or latent onset

[15] EPA, Guidelines for Reproductive Toxicity Risk Assessment, June 1996, available at https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf

> because of the shorter duration of exposure for the P generation. These limitations are shared with the shorter-term 'screening' protocols . . ."

These guidelines reflect EPA's view of the "best available science" for the determination of reproductive and developmental toxicity. As TSCA requires EPA to "use scientific information, technical procedures, measures, methods, protocols, methodologies, or models … in a manner consistent with the best available science" when making prioritization decisions, 15 U.S.C. § 2625(h), EPA must, at a minimum, possess data supporting low-priority designations that satisfy those guidelines' requirements.

In its proposed designations, however, EPA classifies several low-priority candidates as lacking the potential for reproductive and developmental effects based on the absence of maternal and fetal toxicity in limited duration, one-generation screening studies. A prime example is 3-methoxybutyl acetate. According to the dossier for this chemical, EPA deemed this chemical of low concern for developmental toxicity because:

> "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."[16]

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,"[17] 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."[18])

Moreover, the dossier justified the absence of concern for reproductive toxicity on the ground that:

> "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."[19]

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[16] Dossier for 3-Methoxybutyl Acetate) Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2019-0106D =EPA-HQ-OPPT-2019-0106

[17] 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

[18] Id. Pg. 1.

[19] 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

This clearly does not meet EPA's risk assessment guidelines as there is no empirical data on 3-methoxybutyl acetate's reproductive toxicity.

Dibutyl sebacate represents another example. The OECD read-across study cited by EPA followed OECD 414 guidelines (Prenatal Developmental Toxicity Study) and was thus a one-generation study rather than a two-generation test (OECD 421 Reproductive/Developmental Toxicity Screening Test). Under the EPA risk assessment guidelines, a prenatal developmental study that examines fetal development at Day 21 of gestation is too limited to draw overarching conclusions on developmental and reproductive toxicity.

Finally, the dossier for 1,2-hexanediol references four subchronic studies but does not cite any reproductive/developmental studies. (ECHA cites a two-generational read-across study on propylene glycol but EPA did not include this study in its dossier (Table 5) and it would not be considered sufficient under EPA's risk assessment guidelines in any event.) Thus, there are no data to demonstrate the absence of developmental and reproductive hazard.

Our review of the dossiers identified only two chemicals, glucono-delta lactone and dipropylene glycol, for which there may be sufficient data on potential developmental toxicity to satisfy EPA's risk assessment guidelines. According to these criteria, none of the 20 proposed low-priority chemicals has sufficient evidence to establish a low reproductive toxicity hazard.

3. EPA's Determinations that the 20 Chemicals Are Non-Mutagenic Are Based on Insufficient Data

To determine whether chemicals fall within its hazard categories for germ cell mutagenicity, GHS lists several tests that provide relevant data:[20]

List of Validated Mutagenicity/genotoxicity Tests

The table below summarizes a list of mutagenicity tests and genotoxicity tests that could be used for GHS classification. They are grouped by somatic cells/germ cells and in vitro/in vivo.

Test Type	Validated Methods
Germ cell mutagenicity tests in vivo	• **Rodent dominant lethal mutation test (OECD 478)** • **Mouse heritable translocation assay (OECD 485)** • **Transgenic rodent (TGR) somatic and germ cell gene mutation assays (OECD 488)** • **Mouse specific locus test**
Germ cell genotoxicity tests in vivo	• **Sister chromatid exchange analysis in spermatogonia** • **Unscheduled DNA synthesis test (UDS) in testicular cells**

[20] https://www.chemsafetypro.com/Topics/GHS/GHS_Classification_Criteria_for_Germ_Cell_Mutagenicity.html

Somatic cell mutagenicity tests in vivo	• **Mammalian bone marrow micronucleus test (OECD 474)** • **Mammalian bone marrow chromosome aberration test (OECD 475)** • **Mouse spot test (OECD 484)** • **Mammalian erythrocyte micronucleus test (OECD 474)** • **Transgenic rodent (TGR) somatic and germ cell gene mutation assays (OECD 488)**
Somatic cell genotoxicity tests in vivo	• **Liver Unscheduled DNA Synthesis (UDS) in vivo (OECD 486)** • **Mammalian bone marrow sister chromatid exchanges (SCE)**
In vitro mutagenicity tests	• **In vitro mammalian chromosome aberration test (OECD 473)** • **In vitro mammalian cell gene mutation test (OECD 476)** • **Bacterial reverse mutation tests (OECD 471)** • **In vitro micronucleus test (OECD 487)**

Note: The classification of individual substances should be based on the total weight of evidence available, using expert judgement.

Similarly, the EPA Safer Choice Master Criteria state that, to classify a chemical as non-mutagenic, "[e]ffects to be considered include heritable germ cell mutagenicity (including gene mutation and chromosome mutation), germ cell genetic toxicity, and somatic cell mutagenicity or genetic toxicity."[21] The criteria identify several tests that should be conducted to classify a chemical's mutagenicity potential:

> **Genetic Toxicity – Test Methods for GHS Review**
>
> **Per GHS [30], results from multiple, acceptable test methods must be used in conjunction for evaluation of genetic toxicity.**
>
> **– OECD Test Guideline 471 (OPPTS 870.5100): Bacterial Reverse Mutation Test [51, 52];**
>
> **– OECD Test Guideline 473 (OPPTS 870.5375): In vitro Mammalian Chromosome Aberration Test [53, 54];**

[21] EPA, *Safer Choice Program Master Criteria* at 12.

– **OECD Test Guideline 474 (OPPTS 870.5395): Mammalian Erythrocyte Micronucleus Test [55, 56];**

– **OECD Test Guideline 475 (OPPTS 870.5385): Mammalian Bone Marrow Chromosome Aberration Test [57, 58];**

– **OECD Test Guideline 476 (OPPTS 870.5300): In vitro Mammalian Cell Gene Mutation Test [59, 60]; and**

– **OECD Test Guideline 483 (OPPTS 870.5380): Mammalian Spermatogonial Chromosome Aberration Test [61, 62];**

– **OECD Test Guideline 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo [63]. This guideline does NOT substitute in the necessary minimum set for either the gene mutation or the chromosome aberration test.**[22]

In contrast to these testing recommendations, nearly all of the dossiers for the 20 chemicals report limited mutagenicity data that falls short of the GHS and EPA recommendations, as the following examples illustrate:

3-methoxybutyl acetate. The dossier on 3-methoxybutyl acetate describes test results for a bacteria reverse mutation assay in Salmonella typhimurium strains and a study on Chinese hamster lung fibroblasts but does not provide data for the other test systems necessary to apply the GHS and Safer Choice criteria for assessing mutagenicity/genotoxicity hazard.

D-Gluconic acid. The EPA dossier identifies only four genotoxicity tests for this substance:

> "Four in vitro gene mutation studies on two bacteria species indicated negative results for gene mutation with and without metabolic activation (NTP, 2018; OECD, 2004; Litton Bionetics, 1974). Mice exposed to glucono-delta-lactone were negative for chromosomal aberrations for both single and repeated dose exposures (OECD, 2004)." (EPA, p. 24).

EPA discusses these tests in only four sentences (EPA Section 6.1.5), failing to provide any details about the substance tested and its purity, study results, or the outcome of any systematic study evaluation if EPA performed one.

Available information about the four studies calls into question their reliability:

- Litton 1974 has no report provided to the public. The EPA HERO website provides only a single sentence summary, "Compound FDA 71-72, glucono-delta-lactone, was not genetically active, either directly or in the presence of organ homogenates, in any of the in vitro assays employed in this evaluation." [23] There is no information about what assays were considered, the reliability of each assay, the protocols followed etc. Suffice it to say that a report that is not publicly available, over forty years old, with no details should not be cited or used by EPA. However, the information is duplicative of the OECD 2004 report also referenced by EPA, so these should not be treated as separate studies.

[22] EPA, *Safer Choice Program Master Criteria* at 24.

[23] HERO ID 4947757, https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/4947757

- OECD 2004[24] is an OECD SIDS report. The same OECD report is referenced twice by EPA, once for *in vitro* genetic toxicity results (OECD, p. 29), and again for *in vivo* genetic toxicity results (OECD, p. 29-30). For the in vitro tests, OECD identifies only two tests - both from Litton (1974) - one in salmonella typhimurium bacteria, and one in saccharomyces cerevisiae yeast (OECD, p. 29). Both are reported to have negative results – that is, no indication of genetic toxicity. OECD notes that, "the strains used, the concentration tested and positive controls differed from OECD guideline 471" (OECD, p. 29). It is unclear why EPA didn't use its authority to require testing that was compliant with current OECD guidelines.

- OECD 2004 also reports on an in vivo study, also from 1974, as follows, "Sodium gluconate and glucono-delta-lactone were tested for induction of chromosomal aberration in mouse bone marrow cells after an oral single and a 4 days repeated dose administration. At least 200 metaphase cells per mouse were scored (C57BL male mice) and were examined for the presence or absence of chromosomal aberrations (gaps, breaks, translocation, fragments, ring chromosomes and minutes chromosomes). None of the tested substances induced chromosomal aberration (Tatsuo Yamashita et al, Fujisawa Pharmaceutical Co., Ltd. 1974)." In the HERO study summary of the OECD report, EPA notes that, "The data summarized in this report are focused on the environmental and health effects from the gluconate anion and read-across to the lactone but do not deal with specific effects of the cations. Thus, toxicological effects related to the cationic components are not part of the present report."

- NTP 2018 is an Ames bacterial mutagenicity test.[25] This test has about 60% sensitivity, which means that 40% of genotoxic chemicals will be undetected.[26]

In addition, these and other in vitro assays have a notoriously high failure rate, and thus regulators normally review a dozen or more, and where possible combine genotoxicity test results with whole

[24] OECD 2004, HERO ID 2072857 Available at https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/2072857
Full report here: https://hpvchemicals.oecd.org/UI/handler.axd?id=b94cc5f7-de5c-4417-b6c2-f1eb4ffcdb72

[25] NTP report here: https://manticore.niehs.nih.gov/cebssearch/study/002-02207-0001-0000-4
HERO ID 4940109 here: https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/4940109

[26] Walmsley RM, Billinton N. How accurate is in vitro prediction of carcinogenicity?. *Br J Pharmacol*. 2011;162(6):1250–1258. doi:10.1111/j.1476-5381.2010.01131.x
This analysis of the failure rate of the most common in vitro genotoxicity assays reports on the sensitivity and specificity of each test, where sensitivity is the proportion of genotoxic carcinogens that accurately produces positive results in a given test, and specificity is the proportion of non-carcinogens (and ideally non-genotoxic carcinogens) that accurately produces negative results. A test with a low sensitivity figure therefore produces a high proportion of false or misleading negative results – that is, a high rate of failure when trying to detect genotoxic carcinogens. For the purposes of environmental public health protection – which is EPA's mandate and the task of TSCA - it is most important to ensure that the battery of tests will accurately identify a chemical that is potentially genotoxic (true positives), without missing any. That is, the battery of tests should not produce false negatives, or low sensitivity. So, for example, a test with 100% sensitivity correctly identifies all genotoxic carcinogens (true positives). A test with 80% sensitivity detects 80% genotoxic chemicals (true positives) but 20% go undetected (false negatives).

animal repeat-dose toxicity tests in the hopes that the redundancy across tests will increase the accuracy. This approach is reflected in EPA pesticide test requirements.[27]

In summary, EPA's classification of D-Gluconic acid as non-mutagenic/genotoxic is based on three studies, two from 1974 that fail to follow existing approved guidelines, and one in bacteria that is just about as likely as not to correctly identify a genotoxic or carcinogenic chemical. This evidence is inadequate for a determination of mutagenic/genotoxic hazard. As EPA itself has elsewhere recognized, the Agency could not make such a determination without a full battery of in vivo and in vitro genotoxicity tests that are not available for this substance and nearly all other low-priority candidates.

4. EPA's Low Priority Dossiers Fail to Provide Sufficient Data to Classify a Substance as Non-Carcinogenic Under EPA Risk Assessment Guidelines

Under EPA's hazard classification system for low-priority listing, a chemical will be deemed a "low" carcinogenicity hazard where there are "negative studies or robust mechanism-based structure activity relationships." EPA cites the IARC cancer classification system and the GHS classification criteria to support this approach, but in fact these guidelines for interpreting cancer data do not define the evidence necessary for a finding of non-carcinogenicity; they only address how to assess the weight of the evidence for chemicals with positive cancer data. Not mentioned in the dossiers is the classification framework in EPA's own 2005 cancer risk assessment guidelines. According to these guidelines, a determination of "Not Likely to Be Carcinogenic to Humans" requires robust data as follows: [28]

> "This descriptor is appropriate when the available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each mode of action in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic. The judgment may be 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.

[27] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/advances-genetic-toxicology-and-integration-vivo

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

Of the proposed low-priority chemicals, only dipropylene glycol potentially has sufficient evidence to make a determination of carcinogenicity under these criteria. None of the other dossiers report the findings of cancer bioassays on either the low-priority candidate or an analog. Instead, EPA relies mainly on negative genotoxicity assays combined with results from various predictive models. The high degree of uncertainty in using these tools, coupled with the absence of the definitive evidence described in the EPA cancer guidelines, precludes a conclusion that the candidate chemical lacks the potential to be carcinogenic.

5. Although Respiratory Sensitization Is a Required Element of EPA's Hazard Classification System, Data on This Endpoint Are Lacking In Several Dossiers

Consistent with the GHS classification system and EPA's Safer Choice Master Criteria, the EPA framework for evaluating the hazard potential of low-priority candidates requires evidence of the absence of both skin and respiratory sensitization:

		High	Moderate	Low
Skin sensitization		High frequency of sensitization in humans and/or high potency in animals (GHS Category 1A)	Low to moderate frequency of sensitization in humans and/or low to moderate potency in animals (GHS Category 1B)	Adequate data available and not GHS Category 1A or 1B
Respiratory sensitization		Occurrence in humans or evidence of sensitization in humans based on animal or other tests (equivalent to GHS 1A or 1B)	Limited evidence including the presence of structural alerts	Adequate data available indicating lack of respiratory sensitization

However, no respiratory sensitization data are presented for tripropylene glycol, 1,2-hexanediol, 3-methoxybutyl acetate and dibutyl sebacate. This represents a significant data gap for a relevant potential hazard, precluding low-priority listing.

6. EPA Lacks Acute Inhalation Data for Some of the 20 Chemicals and Thus Has No Basis for a Low-Hazard Determination for Inhalation Exposure

The GHS hazard classification system calls for evaluation of acute toxicity by all routes of exposure – oral, dermal and inhalation. Similarly, although EPA's Safer Choice Master Criteria have some significant limitations, as our groups have documented in previous comments to EPA,[29] they do require chemicals

[29] The Master Criteria should be expanded to include several GHS criteria (including skin corrosion, eye irritation and corrosion, single dose toxicity, and respiratory irritation) and endpoints evaluated by the California

to demonstrate acute toxicity above the GHS "low hazard" threshold doses by all routes of exposure and recommend acute toxicity testing by all routes in order to qualify for the Safer Choice label.

Inhalation exposure is typically a more sensitive indicator of acute toxicity than oral and dermal routes because the primary function of the lungs is to transfer gases - specifically oxygen and carbon dioxide - in and out of the blood stream. Only one single cell layer separates the lungs from the blood circulation. In contrast, both the skin and the gut wall act as a barrier many cell layers thick. Thus, studies from these two routes cannot be used to infer an absence of inhalation acute toxicity. However, the dossiers for some of the 20 chemicals do not report acute inhalation toxicity results or only provide data for analogs.

For example, for 3-methoxybutyl acetate, EPA cites only acute oral, dermal and gavage test results. No inhalation toxicity data are referenced even though the dossier notes that "3-methoxybutyl acetate in its pure form is expected to be volatile at ambient temperatures" and "there is an increased potential for absorption through the lungs from inhalation exposure" due to its high water solubility. 3-methoxybutyl acetate Dossier at 6. Moreover, according to the dossier, 3-methoxybutyl acetate has numerous industrial, commercial and consumer uses, so widespread inhalation exposure would be expected.

Dimethyl malonate is another chemical that is "expected to volatilize at ambient temperatures" and therefore workers may be exposed through inhalation of vapors. However, EPA only assessed studies on acute toxicity for oral and dermal exposure.

The absence of acute inhalation data for these chemicals precludes listing them as low-priority.

B. EPA's Low Hazard Determinations Suffer from Numerous Deficiencies in Methodology, Disregard Relevant Data and Misclassify the Studies on Which EPA Relies

1. EPA Has Not Transparently Documented the Quality and Reliability of the Data It Is Relying on for the 20 Low-Priority Candidates

Like other provisions of TSCA, the low-priority listing requirements in section 6(b)(1) are governed by the scientific standards in section 26(h) and (i), under which EPA must employ "the best available science" and base decisions on "the weight of the scientific evidence." EPA has defined "best available science" as follows:

> "Use of best available science involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer reviewed science

Department of Toxic Substance Control (DTSC) in the Safer Consumer Products program. Toxicity thresholds across multiple endpoints should be expanded to be more protective of human health. Environmental toxicity and fate should be expanded significantly to assess potential impacts of SCIL chemicals on ecosystems and the environment. - Daniel Rosenberg, NRDC. See EPA 2018, A Working Approach for Identifying Potential Candidate Chemicals for Prioritization. Available at https://www.epa.gov/sites/production/files/2018-09/documents/publiccommentssummary_dec11_preprioritization_927.pdf

> and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data)."

40 CFR §702.33. It has also defined "weight of the scientific evidence" to mean:

> "…. 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."

Id.

These provisions require EPA to carefully review and document the quality and reliability of the data on which it bases its low-priority determinations. EPA has not met that burden.

In its August 2019 *Approach Document for Screening Hazard Information for Low-priority Substances Under TSCA,*[30] EPA describes the quality metrics it used to evaluate available studies on the low-priority candidates and the process it followed to determine whether these studies meet minimum quality and reliability standards. However, these new criteria are inconsistent with previous criteria EPA has developed for the systematic review of studies on risk evaluation chemicals and reflect a new definition of "weight of the scientific evidence" that departs from the definition included in EPA's risk evaluation regulations to help inform overall conclusions about hazard and risk. The *Approach Document* provides limited explanation of the development process or rationale for the new criteria and does not indicate how, if at all, they represent "the best available science" and "systematic review" process EPA is required to apply under TSCA. Rather, EPA's quality metrics are ad hoc and non-transparent.

Even apart from these concerns, the dossiers for the 20 chemicals provide no explanation of how EPA has applied the *Approach Document* to the studies that form the basis for its low hazard rankings and, indeed, lack any documentation of its evaluations of study quality. Thus, there is no indication whether EPA found quality deficiencies in any of the studies, what these deficiencies might be and why EPA concluded (if it did) that the study was nonetheless sufficiently reliable to support a low-priority listing. This makes it impossible to confirm that the studies supporting EPA's low-priority listings were conducted "in accordance with sound and objective science practices" or that it used a scientifically credible "systematic review method" to evaluate the "strengths, limitations and relevance of each study" and to "identify and evaluate each stream of evidence."

In fact, an examination of studies cited in the dossiers reveals a plethora of quality concerns that EPA has ignored:

1,2-Hexanediol. For the critical endpoint of acute inhalation toxicity, EPA relies on a fatally flawed test for aerosol inhalation and lacks any study for inhalation of vapors, which likely poses greater hazards for this substance. The only study EPA identifies on acute toxicity from inhalation (Table B.1, p. XIV, HERO ID 5076436) is on another substance, pentylene glycol, or 1,2-pentanediol (CASRN 5343-92-0). Additional

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

details about the study are found in the ECHA registration dossier.[31] The study -- an LC50 study in rats – exposed the rats to only two doses (3 mg/L and 7 mg/L) for 4 hours/day as an aerosol (the liquid test chemical was perfused through a spray nozzle). Although described as following OECD Test Guideline (TG) 403,[32] the study in fact was conducted prior to those test guidelines (in 1982, whereas TG403 was adopted in 2009) and departs from them in several significant ways that make a 'low hazard' conclusion unreliable. For example:

- The study had only two doses - 3 and 7 mg/L. Two doses is inadequate to construct a reliable concentration-response relationship. TG403 is clear that a minimum of three doses is required for the main test, and then additional doses can be added if necessary to achieve observable effects (TG403, p. 7).

- The doses were likely far too high to be respirable. TG403 makes clear that the "primary goal is to achieve respirable particle size" because if the test animal cannot breathe in the chemical particles than exposure will not occur, and the test will fail. TG403 further states that "aerosol testing at greater than 2 mg/L should only be attempted if a respirable particle size can be achieved" (TG403, p. 7). TG403 defines respirable to be a mass median aerodynamic diameter (MMAD) of 1 to 4 microns, which is achieved at a limit concentration no higher than 2 mg/L for aerosols (TG403, p. 8). The study provides no evidence or statement regarding the MMAD of the aerosol particles, or that the particle size was respirable. Since the two doses both exceed the TG403 limit, it is reasonable to presume that most of the exposure did not enter the body, making the test biased to the null (failure to find an effect) and effectively useless.

Further, EPA's reliance on an aerosol inhalation study fails to account for the exposures from inhaling chemicals in the form of a vapor. EPA acknowledges that 1,2-hexanediol is expected to be volatile when present as a 'neat' or undiluted substance, making inhaled vapors a possible route of exposure.[33] EPA goes further and notes that, "if inhalation of vapors or aerosols occurs, absorption through the lungs is likely" because of the chemical's high water solubility. Thus, EPA should either require a reliable study that addresses acute inhalation of vapors or acknowledge a data gap for this critical endpoint.

Instead, however, EPA dismisses the hazard of inhaling 1,2-hexanediol vapor with the unsupported and unreferenced statement that the "estimated Henry's Law constant" suggests that, when the chemical is diluted in water, volatilization will be "minimal" and therefore "exposure through breathing vapor is expected to be minimal."[34] EPA dismisses hazards to workers with the same statement.[35] EPA's rationale for the absence of vapor inhalation data is indefensible for several reasons. First, EPA has failed to either define or quantify 'minimal.' For example, it has offered no information on how much of the undiluted chemical will volatilize under all the temperature and pressure conditions in which it is used, and over what duration. Second, as with its use of models and estimates for all 20 low-priority candidates, EPA

[31] European Chemicals Agency (ECHA). 2019. DL-hexane-1,2-diol (CAS #6920-22-5). Available at https://echa.europa.eu/registration-dossier/-/registered-dossier/11614/1http://echa.europa.eu/information-on-chemicals

[32] OECD Test No. 403: Acute Inhalation Toxicity. September 2009. DOI:https://doi.org/10.1787/9789264070608-en Full pdf at https://www.oecd-ilibrary.org/docserver/9789264070608-en.pdf?expires=1573253543&id=id&accname=guest&checksum=25F70FEEE4A42DC1773ABAEE99664A36

[33] 1,2-hexanediol dossier at 6.

[34] 1,2-hexanediol dossier at 6.

[35] *Id.* at 21.

has failed to report on the accuracy or reliability of its "estimated" value for Henry's Law Constant, derived using EPISuitev4.11 modeling. Finally, low exposure is not the same as no exposure and cannot be equated with the absence of risk when there is no experimental data defining the 1,2-hexanediol vapor levels that are acutely toxic.

3-methoxybutyl acetate. Although EPA acknowledges that there are "no traditional neurotoxicity studies" available for this chemical, EPA identifies two pieces of evidence – "relevant endpoints measured in a repeated dose study and predictions by U.S. EPA's ToxCast" – to justify concluding that it "anticipates low concern for neurotoxicity."[36] Neither of these two data sources are sufficient, even when considered together, to establish that 3-methoxybutyl acetate lacks any potential for neurotoxicity.

The first claim cites J-CHECK, 2004. The HERO database (HERO ID 4839287)[37] describes J-CHECK as the "Japanese Chemical Collaborative Knowledge database." Although the HERO entry says the study is in English, in fact only a very short summary is in English and the original study is in Japanese, according to the summary at the link provided in the HERO database.[38] The English summary does not report what functional tests were performed on the treated rats or provide any data tables or other details of the test results, and only says that, "no treatment related effect was observed." An alert at the top of the English summary page warns that, "User should check the details with the original report (in Jpanenese) [sic] for confirmation" because "Data may not be evaluated or assessed by expert and confirmation of test results is needed if these data are used for assessment." There is no indication in the 3-methoxybutyl acetate dossier that EPA translated the Japanese-language original report and confirmed the test results. In this event, EPA should not be using the information for assessment, as the study summary alert makes clear.

The second EPA claim -- that it "search[ed] for predictions by U.S. EPA's ToxCast" -- is meaningless because there are no neurotoxicology data available in ToxCast for 3-methoxybutyl acetate.[39] EPA itself notes that "Assays related to neurological functions were not identified for 3-methoxybutyl acetate in ToxCast (U.S. EPA ToxCast, 2019)."

Since the repeat dose study EPA cites lacks confirming details and ToxCast is irrelevant, there is no basis to conclude that 3-methoxybutyl acetate is lacking in neurotoxicity potential.

Dibutyl Sebacate. EPA's classification of dibutyl sebacate as non-mutagenic/genotoxic is based on two studies. The first summarizes the results of several in vitro tests using the analog dibutyl adipate. Dibutyl adipate showed positive results for chromosomal aberration with metabolic activation at 0.7 mg/mL, the lowest concentration tested. EPA concludes that because cytotoxicity was also observed at this

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[36] 3-methoxybutyl acetate dossier at 17-18.

[37] EPA Health and Environmental Research Online (HERO) database. HERO ID 4839287 https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/4839287

[38] J-CHECK 2004 https://www.nite.go.jp/chem/jcheck/template.action?ano=26691&mno=2-0739&cno=4435-53-4&request_locale=en

[39] See 3-Methoxybutyl acetate, 4435-53-4 | DTXSID2052106, Searched by DSSTox Substance Id.Executive Summary. Available at https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID2052106#exec_sum This link is to the comptox dashboard, which as of August 2019 is where the information is held and updated for ToxCast, Tox21 and EDSP, available at https://comptox.epa.gov/dashboardn

concentration, the positive results were invalid. However, since concentrations below the threshold for cytotoxicity were not tested, there is no basis to conclude that this chemical does not cause chromosomal aberrations.

The second study summarizes two in vivo tests for dibutyl sebacate: one micronucleus study in mice and a sex-linked recessive lethal mutation study on Drosophila. ECHA disregards the results for drosophila, due to "major methodological deficiencies." The micronucleus study receives a score of 4, because the publication only contains a summary of results, and does not include detailed information on method and results. Given the absence of these details, there is no basis to rely on either of the tests.

In short, EPA lacks any reliable test data to support a conclusion that dibutyl sebacate is non-mutagenic/genotoxic.

2. Despite Relying Heavily on Data on Analogs, EPA Has Not Adequately Demonstrated That These Analogs Are Strong Surrogates for Low-Priority Candidates

EPA heavily relies on data on analogs to compensate for the absence of directly relevant data on the low-priority candidates themselves. While there are some circumstances where data on analogs can characterize the effects of an untested chemical with a high level of confidence, there are many other situations where extrapolation from analog data involves considerable uncertainty and testing on the compound of interest is necessary to provide reliable information for hazard evaluation. Since designation of a chemical as low-priority under TSCA requires "*information sufficient to establish*" the lack of potential hazard, reliance on analog data will only be justified where these data are highly likely to be predictive of the health and environmental effects of the low-priority candidate. However, EPA's selections of analogs lack adequate explanation. EPA presents limited information and analysis to justify why the analog is a strong surrogate for the low-priority candidate and fails to identify the Agency's reasons for rejecting other possible analogs that showed reported adverse effects. There are established methods to evaluate the degree of similarity between chemicals. Generally, chemical similarity analysis involves structural descriptors and similarity coefficient calculation; for example, the Tanimoto coefficient is widely used and considered to have high predictive accuracy.[40] However, EPA has not employed these techniques to validate its choice of analogs. The result is a confusing and often internally inconsistent and arbitrary manipulation of data on analogs to bolster inherently weak cases for low-priority listing, as the following examples illustrate.

3-methoxybutyl acetate. EPA determined 3-methoxybutanol to be the best analog for 3-methoxybutyl acetate because it "is the expected alcohol metabolite." 3-methoxybutyl acetate Dossier at 14. However, EPA also stated that "predicted metabolites included carboxylic acid/ether, aldehyde/ether, alcohol/ether, and C2 carboxylic acid" and that possible metabolites included a "C1 aldehyde, ester/ketone, carboxylic acid/alcohol, aldehyde/alcohol, diol, ester/alcohol, and a C1 carboxylic acid." *Id.* at 15. The dossier for 3-methoxybutyl acetate does not indicate whether these other metabolites were also considered as analogs and why they were not chosen. Furthermore, 3-methoxybutyl acetate's ECHA dossier contains a read-across study with 1,3 butanediol, another metabolite of 3-methoxybutyl

[40] 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

acetate. A dose-related reduction in fertility was observed in F2D and F2E generations, so the NOAEL is set at the lowest tested dose of 5000mg/kg. EPA apparently excludes this study because 1,3 butanediol was not the analog of choice, but it does not explain why.

EPA also ignores relevant health risks associated with the analogs that it has selected. EPA fails to note that the Danish Environmental Protection Agency lists 3-methoxybutanol as a category 2 mutagen, or a chemical "suspected of causing genetic defects."[41] EPA has no "quality experimental data" on 3-Methoxybutyl Acetate's carcinogenicity and has acknowledged that it can be metabolized into formaldehyde, a known carcinogen. *See* pp. 31-32 *infra*. Therefore, the mutagenic properties of EPA's selected analog should disqualify 3-methoxybutyl acetate from meeting the low-priority definition.

Dibutyl Sebacate. EPA identifies both dibutyl adipate and diisopropyl sebacate as analogs for dibutyl sebacate. Experimental results for skin irritation available for these two analogs are conflicting: diisopropyl sebacate did not cause dermal irritation in rabbits, while dibutyl adipate did cause dermal irritation in rabbits. Rather than using both studies, EPA justifies its "low" concern designation by determining that diisopropyl sebacate is the "stronger" analog, even though EPA uses dibutyl adipate to assess multiple other endpoints. If there is data available on both analogs, EPA should consider both as opposed to disregarding the most sensitive study.

Moreover, EPA fails to mention that the Endocrine Disruption Exchange, a science-based, not for profit organization that studies the endocrine disrupting effects of chemicals and publishes the results of its findings in peer-reviewed journals, lists dibutyl adipate as a potential endocrine disruptor, a list that is based on evidence of endocrine disruption in scientific studies.[42] Given that EPA has not identified any endocrine studies for dibutyl sebacate, the endocrine concerns associated with one of EPA's selected analogs should preclude a low-priority designation. Dibutyl adipate is also listed as toxic to reproduction and hazardous to the aquatic environment by Japan's Ministry of Economy, Trade and Industry.[43] While EPA uses dibutyl adipate as an analog for both of those endpoints, it does not mention either of those classifications or consider the underlying studies on which they were based, thereby ignoring hazard concerns for its selected analog that undermine its case for low-priority listing.

3. EPA Is Over-Reliant on Modeling in the Absence of Data on the Low-Priority Candidate or an Analog and Repeatedly Misinterprets Its Modeling Results

For several of the low-priority candidates, EPA lacked experimental data for particular endpoints on both the low-priority candidate and potential analogs. In such cases, "EPA relied on publicly available quantitative structure activity relationship (QSAR) models and structural alerts (SA) to" predict carcinogenic potential and other adverse effects.

The last 15 years have witnessed the exponential growth of chemical evaluation methods that involve computational models, tests on cells and proteins, and engineered tissues. However, when it comes to

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[41] https://clp-vejlliste.mst.dk/default.aspx?eng=yes#lblJump

[42] https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list#sname=105-99-7+&searchfor=any&sortby=chemname&action=search&searchcats=all&sortby=chemname; *see also* Fang H, Tong WD, Branham WS, Moland CL, Dial SL, Hong HX, Xie Q, Perkins R, Owens W, Sheehan DM. 2003. Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. Chem Res Toxicol 16(10):1338-1358

[43] https://www.nite.go.jp/chem/english/ghs/13-mhlw-0016e.html

chronic or systemic health effects, these methods still lack the ability to capture the biological processes that occur in whole living organisms. For complex disorders like infertility, autism, Parkinson's disease, and even obesity—all of which can have environmental/chemical contributors—and for key windows of development (from conception to early adulthood), animal-based experimentation remains an essential component to keeping populations safe.

In 2007, the National Academies of Sciences suggested in their groundbreaking report, *Toxicity Testing in the 21st Century*,[44] that several decades would be needed for scientists to develop the necessary biological understanding to completely replace animal tests in our chemical evaluation paradigm. A recent National Academies 2017 report, *Using 21st Century Science to Improve Risk-Related Evaluations*,[45] confirmed that these models and alternative test methods still fail to capture the complete biological information necessary to reliably predict potential adverse effects. If such models and alternative tests identify evidence of a harmful effect, that effect should be presumed in the absence of contrary test data. However, not finding a needle in a haystack doesn't mean one isn't there. Thus, modeling predictions are inadequate, standing alone, to "establish" that a chemical *lacks* potential adverse effects.

As an example, EPA reports that the VEGA model indicates that glucono-delta-lactone has "low potential to be carcinogenic or mutagenic" (p. 24). But two of the four models within VEGA 1.1.4 make predictions with "low reliability" and two with "moderate reliability."[46] Moreover, as GreenScreen has noted, the VEGA model may not identify potential carcinogenicity by the inhalation route because inhalation exposure avoids detoxification by protective nucleophiles (ToxServices 2014).These uncertainties make the model of limited value in establishing the lack of carcinogenicity potential.

Equally troubling, EPA in several instances misinterprets modeling results, concluding that that they demonstrate an absence of concern when in fact they raise red flags. For example, EPA disregarded carcinogenicity structural alerts on glucono-delta-lactone using ISS 2.4 profiler encoded in the QSAR Toolbox 4.3. EPA acknowledges that this QSAR model identifies several potential metabolite alerts, but then postulates without any evidence or support that "these metabolites are expected to be excreted."[47] (As discussed above, EPA takes a similar approach for 3-methoxybutyl acetate, where it acknowledges that "[a]n aldehyde was identified as a potential metabolite alerts" but dismisses this concern because "this metabolite is expected to be excreted.")

In another example, the OncoLogic v8.0 modeling result for glucono-delta-lactone is in fact 'moderate' for carcinogenicity, not 'low' as EPA asserts. EPA states that: "Based on OncoLogic30 v8.0, the lactone function group was listed as marginal (likely to have equivocal carcinogenic activity) by injection but low (unlikely to be carcinogenic) by inhalation, dermal, or oral exposure. Injection is not a relevant exposure pathway for this chemical substance under TSCA." (p. 24) Not only does EPA fail to provide the results of

[44] http://dels.nas.edu/resources/static-assets/materials-based-on-reports/reports-in-brief/Toxicity_Testing_final.pdf

[45] https://www.nap.edu/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations

[46] EPA states, "D-Gluconic acid and its metal salts were processed through all 4 models. ISS 1.0.2 and IRFMN/ISSCAN-GX 1.0.0 predicted the acid to be non-carcinogenic with moderate reliability" (Table B.1, p. XXIX). From this, EPA concludes that, "Overall, D-Gluconic acid and its metal salts are expected not to be carcinogenic on the basis of the VEGA predictions" (Table B.1, p. XXIX).

[47] Glucono-delta-lactone Dossier at 24.

its modeling exercise, but it seems that EPA did not even conduct such an analysis, since in Appendix B, where EPA purports to report a summary of the model results, the only statement provided regarding the OncoLogic v8.0 model output in Table B.1 under "Cancer" is that "OncoLogic currently has no assessment criteria regarding sugar derivatives" and "Structure could not be evaluated by Oncologic" (Table B.1, Cancer, p. XXVIII). Did EPA use the OncoLogic model to assess carcinogenicity or not? If so, what was the result of the analysis? Why has EPA failed to present the results, including the full output of the model analysis? If in fact EPA did use the OncoLogic model, then it should support a "Moderate" carcinogenicity classification, not "Low," as EPA states in its dossier, and this would preclude a finding that glucono-delta-lactone lacks carcinogenicity potential.

4. EPA's Classification System Incorporates a High-Dose Threshold for Reproductive and Developmental Effects but GHS and Other Classification Systems Do Not Include This Approach and EPA Has Failed to Justify It

For both reproductive and developmental effects, EPA's hazard criteria rank chemicals as "low concern" where they demonstrate toxicity only above specified dose levels, as shown below:

	High	Moderate	Low
Oral (mg/kg/day)	< 50	50 – 250	> 250
Dermal (mg/kg/day)	< 100	100 - 500	> 500
Inhalation (vapor, gas, mg/L/day)	< 1	1 - 2.5	> 2.5
Inhalation (dust/mist/fume, mg/L/day)	< 0.1	0.1 - 0.5	> 0.5

Under this approach, low-priority candidates demonstrating adverse reproductive and developmental effects would be classified as lacking "a potential hazard" if these effects are observed only at high doses. However, the U.N. Globally Harmonized System for Classification and Labeling does not utilize this dose-based approach, instead providing only two classifications: Known or Presumed Human Reproductive Toxicant and Suspected Human Reproductive Toxicant. These GHS Categories (also used by GreenScreen) are based on the weight of evidence, not doses where effects occur.[48] Thus, GHS 1A (known) requires evidence in people; GHS 1B (presumed) requires "clear evidence of adverse effects" in animal studies. Where these standards are met, GHS 1A or 1B would apply, regardless of the dose level. (p 186). Prop 65[49] and NTP[50] [51] also base determinations of development/reproductive hazard on weight

[48] https://www.chemsafetypro.com/Topics/GHS/GHS_Classification_Criteria_for_Reproductive_Toxicity.html
[49] OEHHA 1993. Criteria For Recommending Chemicals For Listing As "Known To The State To Cause Reproductive Toxicity https://oehha.ca.gov/media/downloads/proposition-65/proposition-65/dartcriterianov1993.pdf
[50] NTP. Explanation of Levels of Evidence for Reproductive Toxicity.
https://ntp.niehs.nih.gov/ntp/htdocs/levels/09_3566_ntp_reprotox_r1.pdf
[51] NTP 2019. Explanation of Levels of Evidence for Developmental Toxicity.
https://ntp.niehs.nih.gov/ntp/test_info/ntp_devtox20190628.pdf

of evidence. The observation of dose-related effects is considered evidence for reproductive or developmental toxicity, and dose thresholds that may miss such effects are not considered.

To justify a dose cutoff for reproductive and developmental effects, EPA refers to values derived from its criteria for High Production Volume (HPV) chemical categorization, as reflected in the Agency's *Methodology for Risk-Based Prioritization Under ChAMP and the EU REACH criteria for Annex IV (2007).* However, the ChAMP criteria were not intended for definitive low hazard determinations. The first paragraph of the introduction to the *Methodology* states that the criteria have a very limited purpose:

> "Risk-based prioritizations (RBPs) are qualitative evaluations that indicate whether the Office of Pollution Prevention and Toxics (OPPT) considers a HPV chemical or chemical category as a low, medium, or high priority for further assessment or risk management activities. RBPs are interim evaluations that neither constitute a final Agency determination as to risk, nor a determination as to whether sufficient data are available to characterize risk." (EPA 2009, p. 3)[52]

Moreover, the only explanation provided in the *Methodology* for its ranking scheme for developmental and reproductive toxicity is that:

> "The oral values are taken directly from the OPPT criteria for reviewing TSCA 8(e) submissions mentioned in the text. The other values are pro-rated estimates OPPT has calculated to accommodate the various data submitted under the HPV Challenge Program. The estimates are based on the routes of administration differences noted above in the repeated-dose criteria table in Section 3.2."

However, EPA's 1991 Reporting Guide for TSCA section 8(e) does not establish a limit dose for reporting reproductive and developmental effects but advises that such effects are reportable based on their seriousness, regardless of a "judgment of either the actual or potential exposure to the chemical."[53] Moreover, the "pro rated adjustments" EPA describes do not have any biological basis, but simply reflect an extrapolation from a separate set of criteria for classifying repeated-dose toxicity data. [54]

Without a science-based justification, EPA's dose limits for classifying reproductive and development effects as "low hazard" are arbitrary and indefensible. The Agency should instead apply the evidence-based GHS ranking system for these endpoints. This approach would provide protections to potentially

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[52] EPA 2009. Methodology for Risk-Based Prioritization Under ChAMP. Available at https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB2010101039.xhtml

[53] ttps://www.epa.gov/sites/production/files/2015-09/documents/1991guidance.pdf

[54] In addition to ChAMP, EPA also references the EU REACH criteria for Annex IV, which sets out exemptions for minimum risk chemicals, as a basis for setting these hazard ratings. [54]EC 2017. Criteria for Inclusion of Substances in Annex IV of Regulation (EC) No. 1907/2006 https://ec.europa.eu/environment/chemicals/reach/pdf/6a_appendix_1.pdf Under the EU criteria, for a chemical to be considered "minimum risk," the absence of significant toxicological effects in relevant toxicological studies must be demonstrated. Absence of significant toxicological effects means no evidence of reproductive toxicity --

- at ≤ 1000 mg/kg/day by the oral route,
- at ≤ 2000 mg/kg/day by the dermal route or
- at ≤ 20 mg/litre/6h/day for gases or vapours or ≤ 5 mg/litre/6h/day for aerosols or particulates (limit tests) by the inhalation route ,
- nor from the application of relevant (Q)SAR models or other structural alerts.

These values are significantly higher than those set by EPA for low concern.

exposed or susceptible subpopulations, for which findings of reproductive or developmental toxicity at high doses could be of concern because of unique vulnerabilities or elevated exposure levels.

EPA's dossier for dibutyl sebacate (CAS 109-43-3) illustrates the significance of a high-dose limit for determining reproductive toxicity. EPA used read-across data from dibutyl adipate (CAS 105-99-7) as evidence of 'low concern', referencing an OECD 1996 study in its HERO database (EPA Dossier for decanedioic acid 1,10 dibutyl ester at 17-18; OECD 1996; HERO ID 5077960).[55] The EPA dossier states, "No adverse effects were noted at the highest dose tested (1000 mg/kg-day), resulting in a NOAEL of 1000 mg/kg-day" (EPA dossier, p. 17-18). However, the OECD 1996 study references a two-page study report from 1996 that – contrary to EPA's 'no effect' statement - documents the following adverse effects at the highest dose: "In the 1,000 mg/kg group, pup weight on day 0 and 4 of lactation was slightly lower and viability on day 4 of lactation was decreased compared to those of the control group." (OECD 1996, p. 2).[56] The ECHA dossier for dibutyl sebacate describes the same study in its Endpoint Summary for reproductive toxicity, also noting the offspring effects, in addition to a parental NOAEL of 1000 mg/kg-day for reproductive toxicity, and a systemic toxicity NOAEL for the offspring at 300 mg/kg/day.[57]

The ECHA dossier also uses read-across information, but reports on several studies instead of just one, and provides more detail in the study report, although still not very much. Viewing more studies, in more species, tested with more read-across analogs, does, however, make clear that there is a tremendous variability across studies.

For example, one study identifies a reproductive NOAEL that is 3-fold lower (more protective) than the one EPA selected: "One GLP-conform reprotoxicity screening study according to OECD 422 is available, in which male and female Sprague Dawley rats were exposed to Bis(2-ethylhexyl) azelate (CAS 103-24-2) at dose levels of 100, 300 and 1000 mg/kg bw/day (Shirota, 2004). Based on the results of the study, the NOAEL for reproductive toxicity in female Sprague Dawley rats was established at 300 mg/kg bw/day, whereas the NOAEL for male Sprague Dawley rats was set at ≥1000 mg/kg bw/day. In offspring (F1), a NOAEL for systemic toxicity of ≥1000 mg/kg bw/day was derived."[58]

This range of NOAELs and LOAELS for both di-butyl sebacate and its analogs shows that a dose threshold is an arbitrary basis for determining the presence or absence of reproductive toxicity concerns. It also shows that EPA has failed to select the study that supports the most sensitive risk estimate for its 'low priority' determination.

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[55] EPA HERO ID 5077960. OECD 1996 technical report of dibutyl adipate. SIDS Initial Assessment Profile. Available on HERO at https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/5077960
Direct link to report at https://hpvchemicals.oecd.org/ui/handler.axd?id=B8A821EB-06E9-4707-A2BE-7196F79226C7

[56] EPA HERO ID 5077960. OECD 1996 technical report of dibutyl adipate. SIDS Initial Assessment Profile. Available on HERO at https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/5077960
Direct link to report at https://hpvchemicals.oecd.org/ui/handler.axd?id=B8A821EB-06E9-4707-A2BE-7196F79226C7

[57] ECHA refers to the study as (Nagao, 1996) here https://echa.europa.eu/registration-dossier/-/registered-dossier/16127/7/9/1

[58] ECHA dossier https://echa.europa.eu/registration-dossier/-/registered-dossier/16127/7/9/1

A review of the chemical conducted for the Consumer Product Safety Commission (CPSC) this year identified as a data gap that the "available standard toxicology studies were either conducted prior to modern test methods, or are available only based on the summaries in secondary sources."[59] While this data gap applies to the entire evaluation of the chemical, CPSC identified specific problems that compromise the ability to assess reproductive toxicity concerns: "Reproductive: A key limitation is that existing studies either were not conducted according to modern methods (Smith, 1953), or did not expose the males for the full spermatogenic cycle prior to mating (Pfizer, 2014c, as cited by FDA, 2014). In addition, it is unclear whether complete histopathology of the reproductive tract was conducted, even in the guideline study (Pfizer, 2014c, as cited by FDA, 2014). Finally, recently added endpoints reflecting endocrine disruption (e.g., estrus cycle length, anogenital distance) were not investigated." [60]

Simply put, EPA cannot make a low priority determination for this chemical based on a database raising so many questions and concerns.

For 3-methoxybutyl acetate, EPA includes only one study for developmental toxicity, with a NOAEL of 1000 mg/kg. While no reproductive toxicity studies are available, EPA considers concern to be low based on low hazard findings for other health endpoints. However, ECHA contains a two-generation read-across study with 1,3 butanediol, a metabolite of 3-methoxybutyl acetate. A dose-related reduction in fertility was observed in F2D and F2E generations, resulting in a NOAEL of 5000 mg/kg, the lowest tested dose. Again, using an arbitrary dose threshold misses evidence of reproductive toxicity that should preclude a low-priority listing.

5. EPA Misapplies the GHS Criteria for Acute Toxicity

In determining whether a chemical presents "low concern" for acute mammalian toxicity, EPA purports to rely on the *United Nations Globally Harmonized System of Classification and Labelling of Chemicals*. However, EPA misapplies the GHS guidance that it claims to rely upon.

For all of the proposed low-priority designations, EPA identifies the following "low concern" thresholds for acute toxicity:

Oral LD_{50} (mg/kg): >2000
Dermal LD_{50} (mg/kg): >2000
Inhalation LC_{50} (vapor/gas) (mg/L): >20
Inhalation LC_{50} (dust/mist/fume) (mg/L): >5

The GHS Guidance, however, does not reference any "low concern" or "low hazard" classification for acute toxicity. Instead, GHS establishes five "acute toxicity hazard categories," as set forth below:[61]

[59] Toxicity Review of dibutyl sebacate, Prepared by Risk Science Center, Cincinnati, for CPSC, 2019. https://www.cpsc.gov/s3fs-public/ToxicityReviewforDibutylSebacate062019.pdf?xg27lyGY4Phr7CwawZsSWzvjMCVEKp5b
[60] Toxicity Review of dibutyl sebacate, Prepared by Risk Science Center, Cincinnati, for CPSC, 2019. https://www.cpsc.gov/s3fs-public/ToxicityReviewforDibutylSebacate062019.pdf?xg27lyGY4Phr7CwawZsSWzvjMCVEKp5b
[61] GHS Guidance at 117.

Table 3.1.1: Acute toxicity estimate (ATE) values and criteria for acute toxicity hazard categories

Exposure route	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg bodyweight) *See notes (a) and (b)*	ATE ≤ 5	5 < ATE ≤ 50	50 < ATE ≤ 300	300 < ATE ≤ 2000	2000< ATE≤ 5000 *See detailed criteria in Note (g)*
Dermal (mg/kg bodyweight) *See notes (a) and (b)*	ATE ≤ 50	50 < ATE ≤ 200	200 < ATE ≤ 1000	1000 < ATE ≤ 2000	
Gases (ppmV) *See notes (a), (b) and (c)*	ATE ≤ 100	100 < ATE ≤ 500	500 < ATE ≤ 2500	2500 < ATE ≤ 20000	*See detailed criteria in Note (g)*
Vapours (mg/l) *See notes (a), (b), (c), (d) and (e)*	ATE ≤ 0.5	0.5 < ATE ≤ 2.0	2.0 < ATE ≤ 10.0	10.0 < ATE ≤ 20.0	
Dusts and Mists (mg/l) *See notes (a), (b), (c) and (f)*	ATE ≤ 0.05	0.05 < ATE ≤ 0.5	0.5 < ATE ≤ 1.0	1.0 < ATE ≤ 5.0	

Note: Gas concentrations are expressed in parts per million per volume (ppmV).

For its prioritization decisions, EPA appears to have defined all test results in Category 5 in the GHS matrix as "low concern" for acute toxicity. But that ignores the existence and purpose of Category 5, which is an additional classification of concern under the GHS Guidance. According to that Guidance, "[c]riteria for Category 5 are intended to enable the identification of substances which are of relatively low toxicity *but which under certain circumstances may present a danger to vulnerable populations*" at 118 (emphasis added). Notably, chemicals that fall within Category 5 must still bear warning labels to alert the public of their potential risks.[62]

In determining whether a chemical substance is high-priority, EPA must consider whether it "may present an unreasonable risk of injury … including an unreasonable risk to a potentially exposed or susceptible subpopulation." 15 U.S.C. § 2605(b)(1)(B)(i). Therefore, in order to support a low-priority designation, EPA must establish that the chemical *will not* present unreasonable risk to any potentially exposed or susceptible subpopulation. *Id*. § 2605(b)(1)(B)(ii). The GHS Guidance that EPA relies upon states that Category 5 chemicals "may present a danger to vulnerable subpopulations."[63] Yet EPA has classified those chemicals as "low concern" for acute toxicity, and thus to be designated low priority, departing from the GHS recognition that the level of acute toxicity encompassed by Category 5 can pose a threat to vulnerable subpopulations.

This is not an academic concern; EPA's misapplication of the GHS Guidance resulted in the misclassification of at least one of the proposed low-priority chemicals. According to EPA, different oral studies of 3-methoxybutyl acetate reported oral LD_{50}s of 3,000 mg/kg and 4,310 mg/kg.[64] Under the GHS criteria, those values would place the chemical within Category 5, meaning it may present acute toxicity risks to vulnerable subpopulations. Because EPA ignored that category, however, it misclassified the chemical as "low concern for acute toxicity," without any further consideration of its potential risks. *Id.* at 16, 24. Because EPA has not considered the circumstances under which 3-Methoxybutyl Acetate

[62] *Id.* at 124

[63] GHS Guidance at 118

[64] 3-Methoxybutyl Acetate Dossier at 17.

may present unreasonable risks to potentially exposed and susceptible subpopulations, the Agency does not have sufficient information to establish the chemical's low-priority status.

6. EPA Uses Undefined and Unquantified Descriptors to Dismiss Hazard and Exposure Concerns

As detailed in many examples described below, EPA dismisses risks to workers, consumers, and others with vague and unproved statements such as the exposure will be 'minimal,' or the chemical is 'unlikely' to cross a lipid membrane, or it is 'expected' to be excreted. These terms are not defined and not quantified. For instance, EPA never explains its criteria for treating "expected exposures" as "minimal" or how this classification might establish the absence of risk to a person with multiple chemical exposures or across a population that includes elders, infants, and the infirm. EPA also fails to explain the basis on which it is "unlikely" that a chemical would cross a membrane or would be "expected" to be excreted. Such vague and unsubstantiated assertions have no place in a hazard assessment and fail to compensate for data gaps or justify dismissing evidence of hazard that would otherwise preclude a low-priority listing.

Examples include:

- EPA acknowledges that 1,2-hexanediol is volatile, that its vapors can be inhaled and that absorption through the lung is likely. Yet, EPA claims that the volatilization will be 'minimal,' even for workers who may be handling the undiluted and thus highly volatile material. [65]

- EPA states that, "Following metabolism, 1,2-hexanediol and metabolites are expected to be excreted via urine. No accumulation in the body is expected as a result of excretion through efficient metabolic pathways and the formation of soluble degradation products."[66] No supporting evidence or citations are identified. The ECHA statement is similarly lacking in evidence: "Following absorption, 1,2-hexandiol is expected to be detoxified mainly through oxidation and conjugation. 1,2-Hexandiol and metabolites are proposed to distribute rapidly, mainly in blood, liver and kidney, while a large fraction may be excreted quickly via urine, in the form of glucuronide conjugation and parent compound. No accumulation in the body is expected due to efficient metabolic pathways and formation of soluble degradation products (glucose derivatives) with established elimination routes."[67] No data or other evidence is identified, and no quantitative information on the rate and efficiency of absorption, distribution, metabolism or excretion is reported. In fact, EPA specifically says such data do not exist: "quality experimental data found through the literature search on 1,2-hexanediol metabolite formation were limited…"[68]

- EPA states that concern for reproductive toxicity from 3-methoxybutyl acetate is "consider[ed] … to be low based on the low hazard findings for other mammalian endpoints, including but not

[65] 1,2-Hxanediol Dossier at 21.
[66] Id. 14
[67] ECHA registration dossier, DL-hexane-1,2-diol. See Toxicological information; Toxicokinetics, metabolism, and distribution; endpoint summary.
https://echa.europa.eu/registration-dossier/-/registered-dossier/11614/7/2/1
[68] 1,2-hexanediol dossier at. 14

limited to acute toxicity, repeated dose toxicity, and developmental toxicity." Data from other endpoints cannot be used as a proxy for a specific endpoint that lacks its own data.

- EPA also supports its conclusion that dibutyl sebacate poses low hazard for neurotoxicity because other human health hazard endpoints, such as acute toxicity and reproductive toxicity, also have low-hazard findings. EPA identifies no connection between those endpoints and neurotoxicity.

7. EPA Has Dismissed Data That Should Be Considered Evidence of Hazard Under Its Hazard Classification Criteria or Wrongly Relied on Studies That in Fact Show Evidence of Adverse Effects

Some of the data EPA cites in its dossiers refute the absence of hazard claimed by EPA and directly undercut the basis for low-priority listing. Three noteworthy examples are 3-methoxybutyl acetate, where EPA disregarded formation of the toxic cancer-causing metabolite, formaldehyde; D-Gluconic acid, where EPA erroneously characterized modeling results as predicting the absence of carcinogenicity when in fact they predicted the opposite; and 1,2-Hexanediol, where EPA erroneously downgraded test results from "high" or "moderate" to "low" hazard.

3-methoxybutyl acetate. In the dossier for this chemical, EPA states that: "An aldehyde was identified as a potential metabolite alerts; however, this metabolite is expected to be excreted. Further, the Virtual models for property Evaluation of chemicals within a Global Architecture (VEGA) models' results indicate 3-methoxybutyl acetate has low potential to be carcinogenic or mutagenic."[69] As with all of the low-priority candidates, EPA fails to provide the model output or any data other than the names of the models and a single sentence for the results of each model. EPA identifies one of the metabolites as "[a] C1 aldehyde," (p. 15) but fails to note that it is formaldehyde, a known carcinogen.[70] This may be why the 2013 Material Safety Data Sheet for a glazing adhesive made by Henkel lists 3-methoxybutyl acetate as mutagenic.[71] EPA has proposed designating formaldehyde as a high-priority chemical under TSCA, citing carcinogenicity as one of the many bases for that designation.[72]

EPA cannot disregard the toxic metabolites of the low-priority candidates, particularly when there are numerous ways that workers and consumers will be exposed to them. For 3-methoxybutyl acetate, EPA predicts the inhalation of vapor or aerosol directly into the lungs, where it will rapidly enter the blood circulation and from there access all the organs and tissues of the body, including the brain. As EPA states:

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[69] 3-methoxybutyl acetate dossier at 17.

[70] Report on Carcinogens, Fourteenth Edition (2019). Formaldehyde CAS No. 50-00-0, Known to be a human carcinogen. First listed in the Second Annual Report on Carcinogens (1981). https://ntp.niehs.nih.gov/ntp/roc/content/profiles/formaldehyde.pdf

[71] Henkel MSDS 2013. https://www.rshughes.com/wm/p/wm-asis/420505a3362f593bc39c1fcc73fef9f53dc2a935.pdf?uf. Mutagenicity is a known mechanism for carcinogenicity, recognized in EPA's Cancer Guidelines and EPA's Guidelines for Mutagenicity Risk Assessment. EPA 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf

[72] 84 Federal Register 44300 (August 23, 2019).

- "Based on its measured vapor pressure (Table 2), 3-methoxybutyl acetate is expected to be volatile at ambient temperatures and workers may be exposed through inhalation of vapors. If 3-methoxybutyl acetate is in a dilute form, the estimated Henry's Law constant for 3-methoxybutyl acetate indicates volatilization from water and aqueous solutions is likely. Workers may be exposed to 3-methoxybutyl acetate in manufacturing, processing, distribution, use and disposal." (p. 22)
- "EPA identified workers as a potentially exposed or susceptible subpopulation based on greater exposure to 3-methoxybutyl acetate than the general population during manufacturing, processing, distribution, use, or disposal. EPA also identified consumers as a population that may experience greater exposure to 3-methoxybutyl acetate than the general population through use of anti-freeze and de-icing products; cleaning and washing agents; dyes/pigments; and paints and coatings, for example." (Id)
- "If the chemical is in an aerosol product and inhalation exposure occurs, 3-methoxybutyl acetate's absorption from the lungs is likely." (p. 22)

EPA dismisses exposure concerns with the simplistic and unproven statement that "3-Methoxybutyl acetate is expected to be metabolized and excreted, further reducing the duration of exposure" (p. 23) Yet EPA fails to cite any evidence – such as the rate of metabolism and the rate and route of excretion – that would confirm this "expectation." Thus, the potential carcinogenic risks to workers and consumers inhaling 3-methoxybutyl acetate and its carcinogenic metabolite, formaldehyde (also called C1 aldehyde), demonstrate that a low-priority listing is untenable.

D-Gluconic acid. In Section 6.1.6 (p. 24-25) of its dossier on this chemical, EPA states that it lacked "quality experimental data… on glucono-delta-lactone" and therefore instead used information estimated or predicted from various models." EPA concluded that this modeling demonstrated the absence of carcinogenicity potential. In fact, however, it predicted carcinogenicity-related activity that EPA unjustifiably dismissed.

EPA states that: "Based on OncoLogic30 v8.0, the lactone function group was listed as marginal (likely to have equivocal carcinogenic activity) by injection but low (unlikely to be carcinogenic) by inhalation, dermal, or oral exposure. Injection is not a relevant exposure pathway for this chemical substance under TSCA." (p. 24) However, this dismissal of injection dosing studies is in conflict with the generally accepted approach taken by GHS and GreenScreen, authoritative sources that EPA claims to be following. According to a certified GreenScreen of this chemical:

> "In general, inhalation and injection provide the best chance of delivering the largest possible amount of direct-acting reactive chemicals to target tissue because of a lesser absorption barrier and better chance of avoiding detoxification by protective nucleophiles such as glutathione. Exposure to the compound by inhalation is expected to raise the level of concern to MARGINAL. The final level of carcinogenicity concern for this delta-lactone when the anticipated route of exposure is inhalation, is MARGINAL."[73]

[73] Gluconolactone (CAS# 90-80-2) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment. Prepared by ToxServices LLC May 14, 2015. Page 25

Thus, EPA should have identified carcinogenicity evidence for D-Gluconic acid that precludes a low-priority listing. By disregarding the level of concern for carcinogenicity due to injection of this chemical, EPA has misrepresented its potential hazard, and wrongly categorized it as a low-priority substance.

1,2-Hexanediol. EPA identifies three studies on irritation, two from skin exposure and one from eye exposure (Table B.1. Appendix B, Irritation, p. XX-XXI). The eye irritation study – conducted in rabbits – followed standard protocols and is considered GLP-compliant, although it failed to report on the purity of the substance (HERO ID 4729534). According to ECHA: "The substance 1,2-hexanediol was shown to be irritating to rabbit eyes in this test according to ASTM method E 1055-85."[74] In the study, conjunctivitis and chemosis were noted in 3/3 test eyes at the 1-hour post-instillation observation. The effects did not resolve in all test eyes by study day 10. Based on this, 1,2-hexanediol was classified as irritating to eyes, CLP Category 2 (ECHA 2014). For this reason, 1,2-Hexanediol triggers the following EU hazard alerts:

H335 - may cause respiratory irritation

H315 - skin irritation (GHS Category 2, highly irritating)

H319 - eye irritation (GHS Category 2A, highly irritating)

ECHA provides additional study details and results, including this statement: "The corneal injury resolved in all test eyes by study day 14. Iritis was observed in 3/3 test eyes at the 1 hour scoring interval and resolved in all test eyes by day 7. Conjunctivitis and chemosis was noted in 3/3 test eyes at the 1 -hour scoring interval. The effects resolved completely in all test eyes at study day 10."[75] Thus, effects persisted for two weeks after treatment. This is consistent with a "high hazard" classification, according to EPA's criteria, where effects clear between 8 and 21 days (EPA Table 4, p. 13). Yet, EPA downgrades the results: "These results indicate moderate [GHS 2B] to high [GHS 2A] concern for eye irritation (with reversible effects) by 1,2-hexanediol." (EPA, 6.1.10 Eye Irritation, p. 17). In fact, only one of the three adverse endpoints resolved by 8 days, and that was only the day before, on day 7. The other two adverse endpoints were squarely within the "high hazard" category. Thus, EPA misstated the study results and, as a consequence, failed to follow its own criteria. Had EPA properly applied these criteria, 1,2-Hexanediol would be deemed a "high irritation hazard" and would be ineligible for low-priority listing.

C. EPA Fails to Consider Risks to Potentially Exposed or Susceptible Subpopulations

As described above, when considering whether a chemical may present unreasonable risk, and thus cannot be classified as low-priority, EPA must consider risks to "potentially exposed and susceptible subpopulations." 15 U.S.C. § 2605(b)(1)(B). TSCA defines "potentially exposed and susceptible subpopulation" as "a group of individuals within the general population … who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health

[74] European Chemicals Agency (ECHA). 2019. DL-hexane-1,2-diol (CAS #6920-22-5). Available: http://echa.europa.eu/information-on-chemicals.
[75] DL-hexane-1,2-diol, Eye Irritation study (1998): https://echa.europa.eu/registration-dossier/-/registered-dossier/11614/7/4/3

effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly." 15 U.S.C. § 2602(12).

EPA acknowledges that potentially exposed and susceptible subpopulations will be engaged in manufacture and use of and exposed to all 20 low-priority chemicals. However, it fails to factor those populations' increased exposures or susceptibility into its low-priority determinations, relying instead on boilerplate language that dismisses their heightened risks without any underlying analysis. For instance, for populations that face greater chemical exposures, such as workers, EPA repeatedly states that "[w]hile the conditions of use will result in an increase in exposures to certain populations, the consistently low-concern hazard profile and reversible effects of [the chemical] provides sufficient evidence to support this proposed [low priority] finding."[76] EPA cannot classify a chemical as low-priority merely because its effects are reversible, a position that would render many of the health effects routinely considered by EPA irrelevant. Moreover, as designed, the hazard classifications used by EPA to support its low-priority designations apply to the general population, and may not be adequately protective for those who are most exposed or most susceptible to the low-priority candidates. While EPA is mandated by TSCA to consider risks to these vulnerable subpopulations in applying the law's definition of low-priority chemical, EPA arbitrarily assumes that its hazard thresholds will protect against these risks, without considering whether any subpopulations may be exposed to concentrations of the low-priority candidates that studies have found to cause adverse health effects or could be expected to be harmed by concentrations that are without risk to the general population. This is a fundamental flaw in EPA's low-priority listing methodology.

Surprisingly, EPA repeatedly states that it "did not identify populations with greater susceptibility to" the proposed low-priority chemicals.[77] The failure to identify such populations is the result of EPA's failure to look. "There is ample evidence from the literature … of increased [chemical] susceptibility due to age, life stage, preexisting disease, genetic variation, and many other factors that should be incorporated into the TSCA evaluations."[78] Many of the 20 low-priority chemicals have exposure by pregnant women, children, and other subpopulations that have increased susceptibility to a range of health effects. Dibutyl sebacate, for instance, is used in finger paints and modeling clay. However, EPA never evaluates whether those children, pregnant women, and other potentially exposed and susceptible subpopulations would face greater risks, and it does not adjust any of its hazard or risk characterizations to account for their heightened susceptibility. Instead, EPA assumes that those populations would face the exact same risks as the general public, without support and in violation of TSCA's mandate to evaluate and protect potentially most exposed and susceptible populations.

D. EPA Fails to Adequately Assess the Low Priority Chemicals' Environmental Hazards

[76] *See, e.g.,* 3-Methoxybutyl Acetate Dossier at 26; *see also* Dibutyl Sebacate Dossier at 17 (reciting similar language).

[77] *See, e.g.,* 3-Methoxybutyl Acetate Dossier at 18; *see also* Dibutyl Sebacate Dossier at 20.

[78] Koman, P. D., Singla, V., Lam, J., & Woodruff, T. J. (2019). Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. *PLoS biology*, *17*(8), e3000372. doi:10.1371/journal.pbio.3000372.

EPA's system for classifying the environmental hazards of the 20 proposed low-priority chemicals is incomprehensible, and its determinations for individual substances are contrary to the methodology that EPA claims to be applying.

1. EPA's Classification System for Environmental Hazard Is Incomplete, Arbitrary and Contrary to Other Established Systems

Unlike human health endpoints, which EPA divides into "very high," "high," "moderate," and "low" hazard categories, the only classifications for environmental hazard are "low concern," "low concern" (a second time), and "may be low concern." Therefore, it is not clear what results, if any, EPA would consider to present moderate or high hazard.

Moreover, EPA improperly combines acute aquatic toxicity, chronic aquatic toxicity, persistence and bioaccumulation in a single hazard table, and thus merges two distinct hazard endpoints (acute and chronic toxicity), which are intrinsic properties of the chemical, with two distinct physical-chemical characteristics (persistence and bioaccumulation), which describe how the chemical acts under defined conditions such as soil, air, water, temperature. This approach is inconsistent with the GHS Guidance, the GreenScreen for Safer Chemicals methodology,[79] and the best available science, under which chemical hazards and physical-chemical properties are assessed independently of each other. For instance, a chemical's bioaccumulation potential does not dictate whether it poses an acute hazard.

A comparison of EPA's acute aquatic toxicity classifications with those in the GHS Guidance (which EPA purports to rely upon) and the GreenScreen for Safer Chemicals methodology, a broadly used method of comparative chemical hazard assessment, is provided below.

Acute Aquatic Toxicity (LC/EC50)	**GHS**	**GreenScreen**	**EPA**
Below 1 ppm	GHS 1 - "Very toxic to aquatic life," independent of degradation	"Very high" hazard, independent of degradation	"May be of low concern" if the chemical reaches 60% degradation within 10 days
1-10 ppm	GHS 2 - "Toxic to aquatic life," independent of degradation	"High" hazard, independent of degradation	"May be of low concern" if the chemical reaches 60 percent degradation within 10 days
10-100 ppm	GHS 3 - "Harmful to aquatic life," independent of degradation	"Moderate" hazard, independent of degradation	"Low concern" if the chemical reaches 60 percent degradation within 28 days

[79] GreenScreen is a broadly used method of comparative chemical hazard assessment that builds on the EPA's Design for the Environment initiative.

Above 100 ppm	No warning, independent of degradation	"Low" hazard, independent of degradation	"Low concern" if the chemical has a half-life < 60 days

This table reveals two fundamental deficiencies in EPA's prioritization process. First, EPA would permit chemicals that are "very toxic to aquatic life" (per GHS) or "very high hazard" (per GreenScreen) to be classified as "may be low concern." This discrepancy alone provides a sufficient reason to reject EPA's classification of acute aquatic hazards. Second, EPA considers biodegradation in evaluating a chemical's acute aquatic hazard. However, GHS views biodegradation as relevant only to *chronic* aquatic hazards, and GreenScreen evaluates it as a separate chemical characteristic independent of aquatic hazard. EPA's merging of acute hazard and biodegradation has no scientific basis. Acute aquatic toxicity measures effects that are often observed within hours, not days or weeks. If a chemical is acutely toxic, a spill or a release will result in environmental harm before the chemical has an opportunity to biodegrade. EPA's discounting of acute hazards based on biodegradation is thus counter to the "best available science."

A comparison of EPA's chronic aquatic toxicity classifications with those in the GHS Guidance and the GreenScreen for Safer Chemicals methodology is provided below.

Chronic Aquatic Toxicity (LC/EC50)	**GHS**	**Green Screen**	**EPA**
Below 0.1 ppm	"Toxic to aquatic life with long lasting effects" if the chemical reaches 60% degradation within 10 days; otherwise "very toxic to aquatic life with long lasting effects"	"Very High" hazard, independent of degradation	"May be of low concern" if the chemical reaches 60% degradation within 10 days
0.1-1 ppm	"Harmful to aquatic life with long lasting effects" if the chemical reaches 60% degradation within 10 days; otherwise "toxic to aquatic life with long lasting effects"	"High" hazard, independent of degradation	"May be of low concern" if the chemical reaches 60 percent degradation within 10 days
1-10 ppm	N/A	"Moderate" hazard, independent of degradation	"May be of low concern" if the chemical reaches 60 percent degradation within 10 days
Above 10 ppm	N/A	"Low" hazard, independent of degradation	"Low concern" if the chemical reaches 60 percent degradation within 28 days

As with acute aquatic toxicity, EPA's classifications consistently understate the potential for chronic hazards. EPA would classify chemicals that are "toxic to aquatic life with long lasting effects" (per GHS) or that present "very high" hazard (per GreenScreen) as "may be of low concern." EPA provides no support for its departure from accepted hazard ranking systems.

2. EPA Evaluates an Inadequate Range of Ecological Endpoints

When evaluating risks to new chemicals under TSCA, EPA separately evaluates acute and chronic risk to fish, aquatic invertebrates such as daphnia, and algae, with chronic risks to algae measured across multiple algae life cycles. In TSCA risk evaluations, EPA has also considered acute and chronic risks to terrestrial vegetation, birds, and mammals, where relevant. In its low-priority designations, however, EPA fails to address risks to terrestrial species for almost all 20 chemicals, and it often lacks sufficient data on aquatic risks (fish, invertebrate and algae) to support a low-priority designation.

For instance, EPA has no testing of dibutyl sebacate's environmental effects. To assess acute aquatic toxicity, EPA relies upon a single test of an alleged analog, dibutyl adipate, on aquatic invertebrates. From that test, EPA concludes that "dibutyl sebacate is low concern for acute aquatic exposures."[80] There are numerous problems with this conclusion.

First, the test provides no information about toxicity to fish or algae, and thus does not cover critical aquatic endpoints. Second, for the one endpoint it does consider, EPA appears not to have the actual study report, which was conducted by a Japanese authority. Instead, EPA relies on the ECHA summary, ignoring the fact that the summary expressly states the test "was only conducted for 24 hours which is considered as insufficient for assessing the acute toxicity to *Daphnia magna*," the test subject.[81] Third, EPA misrepresents the information presented in the ECHA summary. EPA claims that "[i]nvertebrates exposed to dibutyl adipate had a reported EC50 greater than 5.2 mg/L, which exceeds the water solubility of dibutyl sebacate."[82] That EC50, however, was calculated over a 24-hour period. The GHS Guidance that EPA relies on recommends that acute toxicity to aquatic invertebrates be measured using a 48-hour EC50.[83] EPA's Sustainable Futures program guidance also recommends the use of a 48-hour EC50 for Daphnia.[84] Unmentioned by EPA, the ECHA summary does provide a modeled 48-hour EC50 for dibutyl adipate of 1.6 ml/L, significantly lower than the value cited in EPA's proposed low-priority designation.

Finally, even if the 24-hour EC50 for dibutyl adipate were used, EPA's claim the EC50 "exceeds the water solubility of dibutyl sebacate" is not supported by the record. Instead, EPA's dossier provides multiple values for dibutyl sebacate's water solubility, some of which are lower than the 24-hour EC50 and others of which are higher.[85] In other words, to conclude that dibutyl sebacate presents low ecological concern, EPA misinterpreted a study on an alleged analog that ignores most of the relevant endpoints

[80] Dibutyl Sebacate Dossier at 19.
[81] https://echa.europa.eu/registration-dossier/-/registered-dossier/5939/6/2/4
[82] Dibutyl Sebacate Dossier at 19.
[83] GHS Guidance at 228.
[84] Sustainable Futures / P2 Framework Manual 2012, Estimating Aquatic Toxicity Using ECOSAR at 6-9 (2012).
[85] Dibutyl Sebacate Dossier at 4.

and is "insufficient for assessing the acute toxicity" to the one species it did measure. This is far from the "best available science" that TSCA requires of EPA's prioritization decisions. 15 U.S.C. § 2625(k).

EPA's analysis of 3-methoxybutyl acetate's acute aquatic toxicity is equally flawed. The only study that EPA has of 3-methoxybutyl acetate's toxicity to aquatic vertebrates reported an LC50 of 7.1 mg/L. Under the GHS Guidance that EPA purports to rely upon, this result indicates that the chemical is "toxic to aquatic life."[86] Under GreenScreen, it would in fact be considered a "high" hazard. Initially, EPA attempts to exclude this study from its prioritization decisions, claiming that it "was not of sufficient quality for inclusion in this analysis" because it contained "information written in a foreign language." However, the ECHA summary states that the study is "GLP compliant" and "reliable without restriction."[87] Further, EPA relies on studies written in a foreign language to support low hazard classifications for other chemicals and other endpoints (for example, the English-language summary of a Japanese-language study of 3-methoxybutyl acetate neurotoxicity detailed elsewhere in these comments). EPA cannot selectively ignore only those foreign language studies that indicate grounds for concern.

EPA also states that, even if it considered this study, "this chemical would still indicate low concern for acute aquatic toxicity … because the aquatic toxicity data is accompanied by greater than 60% aerobic biodegradation within 10 days."[88] However, as explained above, biodegradation is only relevant to the characterization of *chronic* aquatic toxicity, not *acute* aquatic toxicity.[89] EPA therefore cannot use 3-methoxybutyl acetate's potential degradation to discount the evidence of acute aquatic toxicity.

III. SUMMARY OF DEFICIENCIES IN PROPOSED LOW-PRIORITY LISTING FOR 3-METHOXYBUTYL ACETATE

For 3-Methoxybutyl Acetate, EPA:

- Dismissed evidence of carcinogenicity without an adequate explanation. EPA acknowledges that 3-Methoxybutyl Acetate can be metabolized into formaldehyde, a carcinogen and proposed high-priority chemical. However, EPA ignores the risks associated with this metabolite based on EPA's conclusory "expect[ation]" that it would be further metabolized and excreted, a statement supported by no further explanation or evidence in the record.
- Erroneously determined that the chemical cannot present an unreasonable risk of acute toxicity to a potentially exposed or susceptible subpopulation. Under the GHS Guidance that EPA purports to apply, the detected oral LD_{50} of 3000 mg/kg "may present a danger to vulnerable populations."
- Dismissed the New Zealand Environmental Protection Authority's classification of the chemical as "acutely toxic" without adequate explanation.

[86] GHS Guidance at 241.
[87] https://echa.europa.eu/registration-dossier/-/registered-dossier/5167/6/2/2/?documentUUID=124a1443-f4f6-4566-87ef-c6234b23ab25
[88] Id at 19.
[89] *See* GHS Guidance at 219-221.

- Erroneously determined that the chemical cannot present an unreasonable risk from repeated exposures to potentially exposed or susceptible subpopulations. Under the GHS Guidance that EPA purports to apply, the NOAEL of 300 mg/kg-day, derived from a 28-day study, indicates potential "damage to organs … through prolonged or repeated exposure."

- Lacked evidence sufficient to conclude that the chemical cannot present an unreasonable risk of neurotoxicity to potentially exposed and susceptible subpopulations. EPA admits that it has "no traditional neurotoxicity studies," but instead of using the TSCA testing and information collection authorities to develop such studies, it proposed a "no unreasonable risk" determination based on (1) a summary of a Japanese repeated dose study and (2) EPA's ToxCast model. However, that summary lacks critical information about the test and ToxCast has no neurodevelopmental assays, an important endpoint for the children and pregnant women that EPA acknowledges could be exposed to the chemical.

- Lacked evidence sufficient to conclude that the chemical cannot present an unreasonable risk of developmental toxicity to potentially exposed and susceptible subpopulations. Instead, EPA dismissed the possibility of developmental effects based on a screening test that constitutes inadequate evidence under EPA's own *Guidelines for Reproductive Toxicity Risk Assessment.*

- Lacked evidence sufficient to conclude that the chemical cannot present an unreasonable risk of reproductive toxicity to potentially exposed or susceptible subpopulations. EPA has no data whatsoever on this endpoint; instead, it improperly dismissed the possibility of reproductive toxicity based on EPA's low hazard determinations for other unrelated endpoints.

- Erroneously determined that the chemical cannot present an unreasonable risk of eye irritation to potentially exposed and susceptible subpopulations. Under the EPA guidance that the Agency purports to apply, the reported animal results of "[eye] swelling[] with lids about half closed" and "colorless eye discharge," lasting up to 48 hours, constitute "moderate," not "low," eye irritation.

- Failed to consider the chemical's potential effects on the immune system.

- Failed to consider the chemical's potential effects on the endocrine system.

- Failed to consider the chemical's effects on exposed or susceptible subpopulations. While EPA states that it "did not identify populations with greater susceptibility to 3-methoxybutyl acetate," the supporting documentation provides no evidence that EPA ever evaluated the susceptibility of children, pregnant women, and other populations that are more susceptible to a broad range of chemical exposures.

- Ignored Safety Data Sheets indicating more severe hazards than those identified by EPA.

- Erroneously determined that the chemical cannot present an unreasonable risk of acute aquatic toxicity, despite a study establishing such risk. EPA rejects the findings of that study based on the chemical's allegedly fast biodegradation, even though biodegradation is relevant only to *chronic* aquatic toxicity and EPA has no data on whether the chemical would biodegrade before resulting in acute risks.

IV. SUMMARY OF DEFICIENCIES IN PROPOSED LOW-PRIORITY LISTING FOR DIBUTYL SEBACATE

For Dibutyl Sebacate, EPA:

- Discounted evidence of unreasonable risk from genotoxicity, including positive results for chromosomal aberration at the lowest concentration tested. EPA claims that those findings present no concern because they occurred at cytotoxic concentrations, but the study did not test any concentrations below the cytotoxicity threshold, meaning that EPA has no basis for concluding that the substance would not be genotoxic at those concentrations as well.
- Neurotoxicity concerns remain a critical data gap. Even short or intermittent exposures to low levels of neurotoxic chemicals like lead and mercury during vulnerable windows of neurodevelopment can lead to permanent debilitating adverse effects including life-long deficits in learning and antisocial behavior. Failure to identify and strictly regulate neurotoxic chemicals is not only failing this generation, but also the next one.
- Lacked evidence sufficient to conclude that the chemical cannot present an unreasonable risk of skin sensitization to potentially exposed or susceptible subpopulations
- Lacked evidence sufficient to conclude that the chemical cannot present an unreasonable risk of reproductive harm to potentially exposed or susceptible subpopulations. Without any data on dibutyl sebacate's reproductive effects, EPA relied on a one-generation study of a purported analog, even though the applicable OECD guidelines call for a study of at least two generations.
- Dismissed the New Zealand Environmental Protection Agency's classification of dibutyl sebacate as a suspected reproductive toxin without any explanation.
- Erroneously determined that the chemical cannot present an unreasonable risk of skin irritation to potentially exposed and susceptible subpopulations, even though the two studies that EPA relied upon reported skin irritation lasting between three and eight days.
- Erroneously determined that the chemical cannot present an unreasonable risk of eye irritation to potentially exposed and susceptible subpopulations. The one study cited by EPA reported eye irritation lasting up to 48 hours, evidence of "moderate," not "low," hazard under EPA's own classification system.
- Failed to consider the chemical's potential effects on the immune system.
- Failed to consider the chemical's potential effects on the endocrine system.
- Ignored Safety Data Sheets indicating more severe hazards than those identified by EPA.
- Failed to consider the chemical's effects on exposed or susceptible subpopulations. While EPA states that it "did not identify populations with greater susceptibility to dibutyl sebacate," it acknowledges that the chemical is found in a range of consumer products used by pregnant women and children. There is no evidence that EPA ever considered whether those and other exposed subpopulations are more susceptible to dibutyl sebacate's health effects.

- Erroneously determined that the chemical cannot present an unreasonable risk of acute aquatic toxicity, despite a study establishing such risk. EPA discounts those findings based on the allegedly low water solubility and high octanol-water partition coefficient ("Log Kow") of dibutyl sebacate, although its own dossier presents a range of potential solubility and Log Kow values, several of which are inconsistent with EPA's explanation. Environment Canada and Health Canada have classified dibutyl sebacate as "inherently toxic in the environment."

CONCLUSION

As discussed in these comments, numerous data gaps, methodological deficiencies and departures from the "best available science" pervade EPA's proposed low-priority designations and affect all the proposed low-priority chemicals. Thus, EPA does not have "information sufficient to establish" that any of these chemicals lack the potential for unreasonable risk under their conditions of use, including risks to potentially exposed and susceptible subpopulations. Unless EPA can provide scientifically valid and sufficient data that establish the absence of potential hazard for all relevant endpoints, it must reclassify the 20 proposed low-priority chemicals as high-priority in accordance with section 6(b)(1)(C)(iii) of TSCA.

Please contact SCHF counsel Bob Sussman at bobsussman1@comcast.net with any questions about these comments.

Respectfully submitted,

Liz Hitchcock
Acting Director
Safer Chemicals Healthy Families

Jonathan Kalmuss-Katz
Staff Attorney
Earthjustice

Patrick MacRoy
Deputy Director
Environmental Health Strategy Center

Jennifer Sass, Ph.D.
Senior Scientist
Natural Resources Defense Council