Erratum: See bottom of p. 23, where "non-threshold" in the original submitted version was corrected to read "threshold."

Environmental Defense Fund
Comments for Toxic Substances Control Act (TSCA)
Science Advisory Committee on Chemicals Review of
Risk Evaluation for 1,4-Dioxane
Docket ID: EPA-HQ-OPPT-2019-0238

Submitted July 19, 2019

Key points of concern for the 1,4-dioxane draft risk evaluation

These comments are being submitted by EDF to assist the TSCA Scientific Advisory Committee on Chemicals (SACC) in its peer review of the draft risk evaluation for 1,4-dioxane. They have been prepared in the very limited time period provided by EPA to submit comments for consideration by the SACC. EDF will be providing comments at the SACC meeting scheduled for July 29-August 2, 2019. EDF reserves the right to supplement these comments at the SACC meeting and to provide additional comments on the risk evaluations on or before the comment period deadline of August 30, 2019. We request that all of our comments be provided to the SACC for its review and consideration.

Summary

In its draft risk evaluation for 1,4-dioxane, the Environmental Protection Agency (EPA) has grossly understated the risks that workers and the environment face from exposure to the chemical. EPA has also abdicated its responsibility under the Toxic Substances Control Act (TSCA) to identify and evaluate the risks the chemical presents to consumers and the general population by excluding from its risk evaluation conditions of use and exposures that are known or reasonably foreseen. EPA has not met its mandatory duty under TSCA to identify and evaluate the risks to vulnerable subpopulations, falsely asserting there is no evidence that certain subpopulations are or may be more susceptible to adverse effects from exposure to the chemical. EPA has utterly failed to utilize the enhanced authorities Congress granted it in 2016 to ensure that it has or obtains robust information on 1,4-dioxane's uses, hazards and exposures, resulting in serious information and analytic gaps and deficiencies that severely undermine the scientific quality of its risk evaluation.

These comments first provide some broad, cross-cutting concerns about the draft risk evaluation as a whole and then present additional comments in the approximate order of the scoping, risk

evaluation and risk determination processes. The order of the comments does not imply relative importance.

Among the major concerns addressed in these comments are the following:

- EPA has ignored evidence that some subpopulations are or may be more susceptible to 1,4-dioxane exposures than the general population (see section 1.A).
- EPA has distorted OSHA requirements and over-relied on personal protective equipment, ignoring its real-world limitations (see section 1.B).
- EPA has, without scientific basis, sought to sow doubt on the use of a linear, non-threshold model for 1,4-dioxane's carcinogenicity, an approach that reflects longstanding agency policy and consensus in the scientific community (see section 1.D).
- EPA has dismissed the liver tumors observed in female mice in the key oral cancer study it uses to extrapolate dermal cancer risks. Its insufficient rationale ignores the IRIS program's basis for including these tumors and its determination that they are the most sensitive endpoint, which has been affirmed through peer review. As a result, cancer risk is significantly understated, a concern also noted by the New Jersey Department of Environmental Protection. (See section 1.E.ii.)
- EPA has excluded *all* exposures and risks to consumers (and to workers from at least one use), based on 1,4-dioxane's presence in such products as a byproduct rather than being intentionally used, a distinction without any basis in science (see section 2.A).
- EPA has excluded from its risk evaluation all general population exposures to 1,4 dioxane, based on EPA's unsupported assertion that existing regulatory programs under other statutes EPA administers have addressed or are in the process of addressing potential risks of 1,4-dioxane in all media pathways (see section 2.B).
- In several instances, EPA's decisions are inconsistent with Agency guidelines (see section 4.B.i).
- EPA fails to consider combined exposures to workers from different routes and sources (see section 4.B.ii).
- EPA has significantly understated the extent of risks to workers it has identified (see section 5).
- EPA's "expectation" of compliance with existing laws and standards as a basis for not finding unreasonable risk is unwarranted (see section 6.A).
- EPA finds no unreasonable risk even when the high-end risk exceeds relevant benchmarks, an approach that is not adequately protective (see section 6.B).
- EPA's allowance of a 1 in 10,000 cancer risk for workers is a major and unwarranted deviation from longstanding agency policy and practice to regulate upon finding cancer risks on the order of 1 in 1 million (see section 6.C).
- EPA's systematic review to support the risk evaluation is flawed and not reflective of best practices (see section 7).

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1. Broad/cross-cutting concerns

A. Insufficient consideration of susceptible populations

In several key sections of the draft, EPA dismisses the potential for some worker subpopulations to be more susceptible to 1,4-dioxane, inappropriately asserting there are none (pp. 21, 150). For example, the Agency states that "the results of the available human health data for all routes of exposure evaluated (i.e., dermal and inhalation) indicate that there is no evidence of increased susceptibility for any single group relative to the general population" (p. 21). Furthermore, the Agency makes the unsupported and clearly erroneous assumption that all workers are "healthy" in its risk characterization (p. 132).

Yet, as EPA acknowledges elsewhere in the draft (p. 108) but fails to address in its analysis of risks, there may be numerous such worker subpopulations, including those with pre-existing conditions that affect the liver or impair metabolism (e.g., nonalcoholic fatty liver disease, which is estimated by the Mayo Clinic to impact between 80-100 million individuals in the United States),[1] or that affect the kidneys, upper respiratory system, or other organs targeted by 1,4-dioxane. Individuals with elevated alcohol intake may also exhibit increased liver sensitivity, yet EPA does not consider this sizeable subpopulation. Additionally, as the Agency acknowledges (on p. 108):

> variations in CYP enzyme expression may contribute to susceptibility because multiple CYP enzymes are involved in metabolism of 1,4-dioxane, including CYP2E1. There are large variations in CYP2E1 expression and functionality in humans (Ligocka et al., 2003) and similar variation in other CYPs involved in 1,4-dioxane metabolism are possible.

EPA also acknowledges that the database for potential reproductive and developmental toxicity of 1,4-dioxane is deficient (p. 108), and hence that "it is not known whether or not pregnant women in the workplace may be at greater risk from exposure." Yet in section 5.3.4 (p. 150), EPA states that it "did not include women of reproductive age or pregnant women who may work with 1,4-dioxane or children ages 16-21 because the acute effects on liver enzymes and CNS effects are not expected to preferentially affect women or developing children." Here, EPA makes an inappropriate leap to claim that a lack of data is equivalent to lack of risk. Pregnant women are expressly identified as a potentially exposed or susceptible subpopulation under TSCA, yet EPA ignores any potential concern and takes no steps to fill this crucial data gap. . (See "key data gaps" below.)

[1] NONALCOHOLIC FATTY LIVER DISEASE, https://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/symptoms-causes/syc-20354567 (last visited Jul. 19, 2019).

B. Overreliance on personal protective equipment and overstatements of OSHA requirements

EPA's risk determinations heavily rely on an assumption that all workers at all points in the value chain and lifecycle of 1,4-dioxane will always use personal protective equipment (gloves and respirators) and that it will be universally effective:

> EPA expects there is compliance with federal and state laws, such as worker protection standards, unless case-specific facts indicate otherwise, and therefore existing OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE consistent with the applicable SDSs in a manner adequate to protect workers (p. 175).

In addition to grossly distorting OSHA authorities and requirements (see below), EPA has provided no data or analysis whatsoever to support these sweeping assumptions. OSHA itself has highlighted the major limitations of reliance on PPE with regard to both extent of use and effectiveness, as has EPA in the recent past. These issues are discussed in detail in previous EDF comments, which are incorporated here by reference.[2]

EPA repeatedly overstates or distorts OSHA's authorities and requirements, claiming that OSHA requires employers to provide PPE (p. 48), implying that OSHA requires the use of respirators for 1,4-dioxane (p. 52), and implying that OSHA's requirement for safety data sheets (SDSs) is sufficient to ensure use of protective measures such as PPE by all downstream users of 1,4-dioxane (p. 60). In fact, OSHA authorities and requirements are quite limited and leave most of their applicability to be decided by employers, not OSHA. Among other things, OSHA regulations do not require that persons comply with SDSs. EDF has described these limitations in detail in a recent series of posts to our EDF Health blog.[3] EDF incorporates those by reference.

In a few places in the draft, EPA acknowledges some of the limitations of PPE (pp. 48, 75), and the preferability of other options higher up in the industrial hygiene hierarchy of controls (pp. 48, 52, 74). But when it comes to determining risk, those limitations and preferences fall away and EPA exclusively relies on "expected" use of PPE to mitigate the risks it has identified.

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[2] *See, e.g.*, EDF Comments on TSCA Review and Scoping for First 10 Chemicals under the Lautenberg Act at 6 (Mar. 15, 2017), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0046; EDF Comments on Significant New Uses of Chemical Substances; Updates to the Hazard Communication Program and Regulatory Framework; Minor Amendments to Reporting Requirements for Premanufacture Notices (Nov. 21, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2014-0650-0052.

[3] *See* Appendix A.

C. Evidence of bias

Throughout the draft, EPA treats differently its determinations of unreasonable risk vs. no unreasonable risk in a consistently skewed manner. Three illustrations of this bias follow:

- EPA's risk determination summary (pp. 21-22) uses direct, unqualified language whenever EPA is asserting it found no unreasonable risk for certain conditions of use. In contrast, EPA's statements describing where it found risk are heavily caveated and tentative. For example, on p. 22 EPA states (emphases added) that it

  > has *preliminarily* concluded that the aforementioned conditions of use present an unreasonable risk of injury to health, as set forth in the risk determination section of this draft risk evaluation. This *draft* document's *preliminarily* [sic] determination of unreasonable risk *does not mean that this is EPA's final conclusion. EPA will consider further input through scientific and public review.*

  No such caveats accompany the statements of no unreasonable risk in the preceding and following paragraphs of that key section.

- In the summary table (Table 6-1, pp. 157-175) that provides EPA's risk determinations, each of the "Risk Considerations" sections repeatedly emphasizes those factors EPA believes overestimate the risk. In contrast, EPA relegates discussion of any factors that could lead to underestimation to less prominent sections of the draft. For example, on p. 55 (emphasis added) EPA acknowledges that the manufacturing worker exposure data on which it relies

  > mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls to provide context. EPA assumed that the 2016 BASF data are PBZ measurements relevant to worker activities and are also 8-hour TWA measurements. *This assumption could underestimate exposures*. The sampling rate was missing for some of the 2016 data, so EPA assumed the same sampling rate was applied for other data in the set. It is uncertain to what extent the limited monitoring data used to estimate inhalation exposures for this scenario that could be representative of occupational exposures in other manufacturing facilities of 1,4-dioxane.

  None of these factors is mentioned in either the "Assumptions and Key Sources of Uncertainty" section (pp. 145-150) or in the final summary risk determinations in Table 6-1.

- EPA states that the degree of confidence or uncertainty in the data it has will be a factor in making its risk determinations (pp. 152, 154), but never explains how this will factor in

or which way it will cut, which renders its application wholly arbitrary. We have one indication, however: On p. 169 EPA invokes the poor quality of its data as a basis for concluding there is no unreasonable risk to ONUs. EPA took no steps to require the development of better data; instead it opted to equate this lack of sufficient data with affirmative evidence of no unreasonable risk.

It also appears significant that the only place in the entire draft risk evaluation where EPA uses boldfaced text to emphasize its conclusion is on p. 101, to highlight that existing data do "**not** support a mutagenic mode of action hypothesis at low doses in vivo" (emphasis in original). This boldfacing of a statement unsupported by scientific consensus (see sec. 1.D.), is further evidence of the Agency's bias.

D. Fomenting doubt

EPA goes to great lengths to cast doubt on the appropriateness of applying a linear/non-threshold mode of action (MOA) for 1,4-dioxane's carcinogenicity (ie: a mutagenic MOA), despite longstanding policy and support for its use in prior reviews. For example, in a 2013 report, the Michigan Department of Environmental Quality Toxics Steering Committee stated that "the currently available scientific information regarding the carcinogenicity of 1,4-dioxane … are insufficient to deviate from the U.S. EPA's default assumption of linearity for developing a cancer potency factor."[4] Similarly, the New Jersey Department of Environmental Protection stated that "the available data are not sufficient to establish significant biological support for a non-linear (threshold) mode of action."[5] EPA's 2013 IRIS assessment of 1,4-dioxane also concluded that "the default linear extrapolation should be utilized to estimate the cancer risk estimates."[6]

In certain sections of this risk evaluation, EPA does indeed present similar conclusions, stating that "evidence is not sufficient to support a MOA of cytotoxicity followed by sustained cell proliferation as a required precursor to tumor formation related to the metabolic saturation and accumulation of the parent compound, 1,4-dioxane" (p. 101).

Yet, in other sections, EPA inflates the degree of uncertainty regarding this proposed MOA:

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[4] Mich. Dep't of Envtl. Quality, Toxics Steering Group, 1,4-Dioxane Subcomm., Review of a 1,4-Dioxane Presentation by Michael Dourson, Ph.D. on October 8, 2013 (Feb. 2015), https://www.michigan.gov/documents/deq/deq-aqd-toxics-14-DioxaneTSG_Report_2015_487415_7.pdf.

[5] N.J. Dep't of Envtl. Protection, Response to Public Input on Draft Interim Ground Water Quality Criteria and Draft Interim Practical Quantitation Levels for Eleven Chemicals at pp. 11-17, https://www.state.nj.us/dep/dsr/supportdocs/11-chemicals-response.pdf.

[6] *See* U.S. EPA, IRIS, *Toxicological Review of 1,4-Dioxane (With Inhalation Update)* at p. 137 (Sept. 2013), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf.

- In section 5.3.3 (p. 149), EPA states that "the main source of uncertainty for human health hazard is the mode of action (MOA) and the selection of linear or nonlinear models for BMD modeling to determine the dose-response relationship."
- In section 5.3.4 (p. 150), EPA states that "there was a high degree of uncertainty in any of the MOA hypotheses considered in this evaluation (e.g., mutagenic mode of action or threshold response to cytotoxicity and regenerative hyperplasia for liver tumors).

To perpetuate this manufactured uncertainty, EPA:

(1) Distorts conclusions from independent scientific publications: Based on the results of their *in vivo* gene mutation assay, Gi et al. 2018 conclude that "1,4-dioxane is a genotoxic hepatocarcinogen and induces hepatocarcinogenesis through a mutagenic MOA."[7] However, in this risk evaluation, EPA has instead decided that "the weight of scientific evidence supports that 1,4-dioxane is not mutagenic" (p. 96). This conclusion in direct contradiction to the authors' own conclusions and is based on a "weight of evidence" approach that EPA apparently utilized but has failed to appropriately explain.

(2) Contradicts its own guidelines by presenting modeling results both with and without liver tumors: As further described below (see *Inconsistencies with Agency Guidelines*), the decision to present both "the best fit of the threshold and linear models applied to tumor data" (p. 101) is in conflict with EPA Cancer Risk Assessment Guidelines, which clearly state that only when "alternative approaches have significant biological support" should an "assessment...present results using alternative approaches."[8] EPA seemingly intends to open the door to questioning of the non-threshold approach, despite longstanding consensus on this issue from the scientific community.

E. Lack of transparency

i. Missing citations, sources, & tables

Throughout the draft EPA cites sources that are not publicly accessible, including a number of key EPA documents. They are not in the docket, the HERO entries for them lack hyperlinks, and we often have been unable to locate them through internet searches. Five examples:

(1) Bronaugh 1982, which EPA cites 16 times as the basis for its skin absorption estimates, is a chapter in a book that we have been unable to locate and that EPA has not provided in response to a request we made on July 10.

[7] Gi, Min, et al., *In vivo positive mutagenicity of 1,4-dioxane and quantitative analysis of its mutagenicity and carcinogenicity in rats*, 92.10 ARCHIVES OF TOXICOLOGY Vol. 3207-221 (Oct. 2018), https://link.springer.com/article/10.1007/s00204-018-2282-0.

[8] U.S. EPA, *Guidelines for Carcinogen Risk Assessment* at p. 1-15 (Mar. 2005), https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

(2) USEPA, 2018a, which EPA used to estimate exposures to 1,4-dioxane in spray foam applications in the absence of any monitoring data (p. 68).
(3) McConnell, 2013, a technical report which EPA uses to describe cytotoxicity as a potential MOA of liver toxicity and cancer.
(4) BASF 2016 and BASF 2018. The former includes no link in HERO. The latter includes a link, which is routed to an "error" in regulations.gov.
(5) JBRC, 1998, a 2-year animal study conducted in Japan, which EPA cites over 30 times.

EPA also omits a table explaining the calculations for section 4.2.6.2.5: Chronic Non-Cancer POD for Dermal Exposures extrapolated from Chronic Inhalation Studies (p. 117). This table should be included to ensure transparency.

ii. Insufficient justifications for key decisions

Table 4-12 (p. 126) contains the oral and associated dermal cancer slope factors (CSF) that EPA considers for its risk characterization. Included in this table are data for male and female rats as well as male mice from Kano et al. (2009). However, missing from this table is any mention of the hepatocelluar tumors observed in female mice in the Kano et al. (2009) study. This omission is highly problematic, given that in the 2013 IRIS assessment, EPA selected this as the most sensitive endpoint and the basis for the oral CSF.

In the current risk evaluation, EPA justifies its decision to omit the female mouse liver tumors by stating that "female mouse hepatocellular carcinoma data from Kano et al. (2009) were not modeled due to the difficulties that were previously noted in the US EPA (2013c) IRIS assessment" (p. 334). However, EPA fails to mention that IRIS was able to resolve this issue by "[applying] other BMD models...to the female mouse liver tumor dataset to achieve an adequate fit."[9] Overall, EPA has not provided sufficient justification for its decision to drop the female mouse liver data, which had previously been identified by the IRIS program (and supported by internal and external peer-reviewers) as the most sensitive endpoint and the basis for the oral CSF.

This decision is highly consequential. In the 2013 IRIS assessment, EPA estimates an oral CSF of 0.1 (mg/kg/day), based on these female mouse liver tumor data. By contrast, in this risk evaluation, EPA estimates an oral CSF of 0.021 (mg/kg/day), based on combined tumors in male rats (Table 4-12) – *approximately 5-fold less protective*.

[9] U.S. EPA, IRIS, *Toxicological Review of 1,4-Dioxane (With Inhalation Update)* at p. 138 (Sept. 2013), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf.

We note that similar concerns were raised by the New Jersey Department of Environmental Protection in its July 9, 2019 comments on the draft risk evaluation,[10] and urge that careful attention be paid to this issue by the SACC peer review panel.

In several sections of the document, EPA does not provide sufficient support for key analytical and modeling decisions it has made. For example, on pages 332-333, the Agency indicates that distinct p-value thresholds were used to judge goodness-of-fit for cancer (α=0.05) vs. non-cancer (α=0.1) models. EPA Benchmark Dose Modeling Guidelines "recommend that α=0.1 be used to compute the critical value for goodness of fit…[except] when there is a priori reason to prefer a specific model."[11] In this risk evaluation, however, EPA has provided no justification for choosing an alternative threshold for the cancer model.

2. Exclusions of conditions of use and exposures

A. Exclusion of exposures when 1,4-dioxane is present as a byproduct

EPA has excluded *all* exposures and risks to consumers (and to workers from at least one industrial use: closed system functional fluids), based on 1,4-dioxane's presence in such products as a byproduct rather than being intentionally used. This distinction has no basis in TSCA, which never differentiates between the intentional and byproduct presence of a chemical. TSCA requires EPA to evaluate the risks of all known and reasonably foreseen uses of a chemical, which clearly encompass byproducts. Nor does the distinction have any basis in science, as byproducts can expose people and the environment just as surely as intentionally used chemicals. EPA's exclusion will result in a deficient and erroneous evaluation and determination of the chemical's risks.

Instead EPA asserts it can and will evaluate the risks of 1,4-dioxane in the risk evaluations for the ethoxylated chemicals that give risk to it as a byproduct (p. 28). But there are dozens or hundreds of such chemicals used in dozens or hundreds of types of consumer, commercial and industrial products, as EPA described in its scope document:[12]

> 1,4-Dioxane may be produced as a reaction by-product, particularly in chemicals which are produced by ethoxylation. These include alkyl ether sulphates (AES, anionic surfactants) and other ethoxylated substances, such as alkyl, alkylphenol and fatty amine ethoxylates; polyethylene glycols and their esters; and sorbitan

[10] N.J. Dep't of Envtl. Protection Comment on Draft Risk Evaluation for 1,4-Dioxane, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0014.
[11] U.S. EPA, *Benchmark Dose Technical Guidance* at p. 33 (June 2012), https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf.
[12] U.S. EPA, *Scope of the Risk Evaluation for 1,4-Dioxane* at p. 21 (June 2017), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0049.

> ester ethoxylates. Therefore, 1,4-dioxane may be present at residual concentrations in commercial and consumer products that contain ethoxylated chemicals. Examples of products potentially containing 1,4-dioxane as a residual contaminant are paints, coatings, lacquers, ethylene glycol-based antifreeze coolants, spray polyurethane foam, household detergents, cosmetics/toiletries, textile dyes, pharmaceuticals, foods, agricultural and veterinary products.

EPA's approach means not only that this chemical's risks will not be evaluated for many years, but that a full picture of its risks from all exposure sources will still be lacking if its evaluation is broken into dozens or hundreds of small pieces -- clearly not what Congress intended.

B. Exclusions based on other statutes

Referencing its earlier problem formulation, EPA has excluded from its risk evaluation all general population exposures to 1,4-dioxane, based on EPA's assertion -- unsupported by any actual data or analysis -- that "the existing regulatory programs and associated analytical processes [under the other statutes EPA administers] have addressed or are in the process of addressing potential risks of 1,4-dioxane that may be present in various media pathways (e.g., air, water, land) for the general population" (p. 28; see also pp., 40, 156).

Aside from the absent legal basis, these exclusions present significant health concerns. For example, in the problem formulation for 1,4-dioxane (pp. 43-44), EPA explicitly relies on the Clean Water Act (CWA) and the Safe Drinking Water Act (SDWA) to dismiss the need to assess exposures to 1,4-dioxane in water. Yet under the CWA EPA has not to date recommended a human health water quality criterion for 1,4-dioxane, and its process and timeline for doing so are highly uncertain. In the absence of a recommended criterion from EPA, only a single state (CO) has adopted a health-based water quality criterion for 1,4-dioxane. EPA's reliance on the SDWA is also unwarranted because 1,4-dioxane has only been listed on the Contaminant Candidate List (CCL). The CCL is a list of *unregulated* contaminants that are known or anticipated to occur in public water systems and that EPA indicates *may* need regulation.[13] In order to establish an enforceable limit, EPA would have to undertake a number of procedures that have not been undertaken for 1,4-dioxane.[14]

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[13] 42 U.S.C. § 300g-1(b)(1)(B)(i); *see also* BASIC INFORMATION ON THE CCL AND REGULATORY DETERMINATION, https://www.epa.gov/ccl/basic-information-ccl-and-regulatory-determination (last visited Jul. 19, 2019).

[14] 42 U.S.C. § 300g-1(b)(1)(B)(ii), (E); *see also* BASIC INFORMATION ON THE CCL AND REGULATORY DETERMINATION, https://www.epa.gov/ccl/basic-information-ccl-and-regulatory-determination (last visited Jul. 19, 2019). EPA has yet to make a regulatory determination on whether even to initiate a rulemaking, let alone initiate the rulemaking and propose and finalize a rule.

The exposures EPA is ignoring are far from trivial. Based on the most recent data from EPA's Toxics Release Inventory (TRI) and National Emissions Inventory (NEI), despite any regulations under other laws facilities release nearly 640,000 pounds annually of 1,4-dioxane to air, water and land. EPA's approach effectively reduces this quantity to zero.

Moreover, 1,4-dioxane is widely detected in public water systems (PWS). In the Third Unregulated Contaminant Monitoring Rule (UCMR3),[15] 1,4-dioxane was found in 21% of the 4864 PWS, and was in exceedance of EPA's own health-based reference value of 0.35 ug/L (corresponding to a cancer risk level of one in one million) in 341 (6.9%) of the PWS sampled. Not only are elevated levels in drinking water of concern; so is exposure by inhalation when people use water at elevated temperatures (e.g., while cooking, bathing or showering).[16]

C. Collapse of varied uses into a single category/single scenario

EPA lumps together a highly diverse set of uses as "industrial uses" (p. 58). They encompass a huge array of sectors, from textiles to agricultural chemicals to pharmaceuticals, and very different functional uses, from solvent to catalyst to intermediate to wetting agent. EPA asserts without providing any support that all such operations "are expected" to be similar.

Beyond this, EPA has used single scenarios to represent each of the following activities despite their varied nature: all processing scenarios other than repackaging (p. 163); all intermediate use scenarios (p. 165); all open system functional fluid use scenarios (p. 166); all laboratory chemicals use scenarios (p. 168); and all disposal scenarios (p. 175). EPA has provided no data or analysis to demonstrate that these scenarios are representative of other scenarios within a grouping or otherwise ensure a health-protective approach.

3. Key data gaps

Under the 2016 reforms to TSCA, Congress enhanced EPA's authority to require submission of existing information and development of new information, including on products and workplace exposures. Despite the major gaps identified below and others that EDF and other stakeholders have identified over the past 2.5 years, EPA made no effort whatsoever to use these authorities to obtain critical exposure information on 1,4-dioxane.

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[15] *See* U.S. EPA, *The Third Unregulated Contaminant Monitoring Rule (UCMR 3): Data Summary* (June 2017), https://www.epa.gov/sites/production/files/2017-02/documents/ucmr3-data-summary-january-2017.pdf.

[16] EPA cited this exposure in its problem formulation (p. 31), but made no mention of it in the draft risk evaluation.

A. Environment

i. Dearth of environmental monitoring data

- EPA states that "recent monitoring data on ambient surface water levels indicate relatively low levels" (p. 213) but never provides any data.
- EPA states: "Limited sediment monitoring data for 1,4-dioxane that are available suggest that 1,4-dioxane is present in sediments" (pp. 131, 211). But no such data are presented in the draft risk evaluation or the preceding problem formulation document.

ii. Dearth of environmental fate data

EPA appears to have identified only one study providing measured values for environmental fate and transport of 1,4-dioxane: a microcosm study on soil biodegradation (p. 44). As a result, it relies on model estimate for all other fate and transport parameters.

iii. Dearth of ecotoxicity data

The only ecotoxicity data EPA has is for aquatic organisms (fish, algae, water flea); it lacks any such data for soil- or sediment dwelling organisms or terrestrial or avian species. Moreover, EPA has no aquatic chronic toxicity data except for fish. Despite these major gaps, EPA repeatedly makes sweeping statements about the lack of any unreasonable risks to the environment as a whole (pp. 21, 156).

B. Human Health

i. Dearth of product/use concentration data

- Open system functional fluids: EPA claims it derived fluid concentrations from available SDSs (p. 62), but none of the relevant cited SDSs that are publicly accessible makes any mention of 1,4-dioxane as a constituent.
- Spray foam application: Only one of the several SDSs EPA cites for this use (p. 68) makes any mention of 1,4-dioxane as a constituent, so EPA's entire exposure analysis rests on this one source and value, precluding any ability to know whether EPA's analysis is at all representative of a large industry that entails, by EPA's estimate, nearly 180,000 workers (p. 68).

ii. Limited, unrepresentative inhalation exposure data for workers

- EPA's sources of workplace exposure data are from selective, unrepresentative sources; lack critical detail on which processes, exposure sources and worker activities they represent; and are insufficient to understand the distribution of exposures in a given setting (pp. 55, 57, 60, 62, 65, 67, 69-74, 146-7).

- Industrial uses: EPA lumps together a highly diverse set of uses as "industrial uses" (p. 58). They encompass a huge array of sectors, from textiles to agricultural chemicals to pharmaceuticals, and very different functional uses, from solvent to catalyst to intermediate to wetting agent. EPA asserts without providing any support that all such operations "are expected" to be similar. EPA's only source of worker exposure data for this broad swath of uses is an EU risk assessment that looked only at the pharma sector and use as a solvent (p. 59). That source provided no detail as to how the data were calculated or what percentile they represent.
- Open system functional fluids: EPA's cited source (Burton and Driscoll 1997) is a NIOSH site report motivated by worker concern over fungi- and bacteria-contaminated synthetic metal–working fluids (MWF). It entailed no direct measurements of 1,4-dioxane, only synthetic MWF and it is not clear the fluids at this site even contained the chemical (p 61).
- Spray foam application: EPA lacks any monitoring data (pp. 67-68, Table 3-17). EPA says it estimated values using an EPA exposure scenario document (USEPA 2018a) that is not publicly accessible (p. 68). EPA also employed modeling that it asserts is "conservative" because it assumes activities take place "indoors, without engineering controls, and in an open-system environment where vapors freely escape." Yet all of these conditions may well characterize spray foam application, which takes place in myriad houses and other buildings
- Printing inks: EPA's analysis of worker exposure to printing inks is based on a single air sample reported in a 2016 paper; despite the fact that the authors and other researchers note that the concentration could well be an underestimate (p. 70), EPA asserts it is likely an overestimate (p. 71).

iii. Failure to adequately consider other authoritative sources of workplace inhalation exposure data

a. EPA references OSHA monitoring data, but does not incorporate them into its exposure assessment.

- EPA's 1,4-dioxane Problem Formulation refers to OSHA data collected between 2002 and 2016 as "key data."[17]
- However, EPA inappropriately excludes these data due merely to challenges it experienced in downloading the data from OSHA's online platform. The data received a score of only 8 for Applicability because, according to EPA: "Looks like it should be an excel file with exposure data, but it's all smooshed together in

[17] U.S. EPA, *Problem Formulation of the Risk Evaluation for 1,4-Dioxane CASRN: 123-91-1* at pp. 30, 69 (May 2018), https://www.epa.gov/sites/production/files/2018-06/documents/14-dioxane_problem_formulation_5-31-18.pdf.

a text file and not useful." That low score pulled the overall score assigned to the OSHA data into the Unacceptable range.[18] (See section 7 in these comments for more discussion.)

- Our own search of the OSHA Chemical Exposure Health Data yielded 475 air samples for 1,4-dioxane between 1987-2012.[19] The OSHA PEL for 1,4-dioxane of 100 ppm (8-hour, TWA) was last updated in 1989 (p. 194), so workplace monitoring data after 1989 are likely relevant.

b. Exclusions of relevant data from the 2002 EU Risk Assessment:[20]

- For Industrial Uses, EPA excludes the highest exposure point (184 mg/m^3) from the 2002 EU Risk Assessment, asserting but not adequately explaining why it considers the value "is likely an outlier" (p. 264).
- While it does not appear that EPA assessed cleaning agents and paint as end uses of 1,4-dioxane at all, the EU Risk Assessment did so and found the chemical's use as a cleaning agent, in particular, to be a significant exposure source:
    - For 6-8-hour exposure, the EU Risk Assessment found the reasonable worst case to be 50 mg/m^3 and the typical concentration to be 15 mg/m^3, which are considerably higher than the Central Tendency ADCs and High-end ADCs EPA relies on for all of its exposure scenarios (see Table 5-5 on p. 137).
    - "Repeated-dose toxicity and carcinogenicity after combined (i.e. respiratory and dermal) exposure at the workplace cannot be excluded for the scenario 'formulation' and the subscenario 'use in cleaning agents.'"[21]

iv. Reliance on extremely limited industry workplace inhalation data from a single site

For its Manufacturing scenario, EPA chose to use only data it received from BASF, comprised of just 30 samples from a single manufacturing site in Zachary, Louisiana, which closed in 2018. In doing so, EPA has assumed these data to be representative of all U.S. manufacturing (see pp. 254-257).

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[18] U.S. EPA, *Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data* at p. 105 (June 2019), https://www.epa.gov/sites/production/files/2019-06/documents/4_14-d_supplemental_-_data_quality_evaluation_environmental_release_and_occupational_exposure_06272019.pdf.

[19] SAMPLE DATA SEARCH RESULT, https://www.osha.gov/pls/samp/sampling_search.search?establishment=&city=&state=--&zip=&startyear=&endyear=&sic=&naics=&substance=dioxane&imis=&beginresult=&endresult=&p_start=120&p_finish=140&p_sort=&p_desc=asc&p_direction=Prev&p_show=20 (last visited Jul. 19, 2019).

[20] European Chemicals Bureau, *European Union Risk Assessment Report: 1,4-dioxane* (2002), https://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa.

[21] *Id.* at 99.

- While the 2016 BASF data are summarized in Appendix G, EPA does not provide access to the original source; no link is provided in the HERO entry for this source.
- Further, EPA makes several assumptions about these data, which appear not to have been confirmed with BASF. While EPA first states: "Occupational exposures to 1,4-dioxane during manufacturing were estimated by evaluating full-shift, personal breathing zone (PBZ) monitoring data obtained by BASF during internal industrial hygiene (IH) studies," (p. 54), it later states:
    - "EPA assumed that the 2016 BASF data are PBZ measurements relevant to worker activities and are also 8-hour TWA measurements" (p. 55, emphasis added), and
    - "EPA assumed that these monitoring data were originated via PBZ measurements" (p. 254, emphasis added).
- These data have other serious limitations, as EPA acknowledges: "The data sets used mostly lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls to provide context" (p. 55).
- EPA scored the 2016 BASF and 2017 BASF data as 1.3 and 1.7, , respectively, in its systematic review.[22] Several questions arise:
    - 2016 BASF data: Why did EPA assign a score of 1 to "Sample Size" and included a note indicating "Representative sample size," when the data set comprised only 28 samples from a single site? In the Risk Evaluation itself EPA acknowledges that these data are unlikely to be representative: "It is uncertain to what extent the limited monitoring data used to estimate inhalation exposures for this scenario that could be representative of occupational exposures in other manufacturing facilities of 1,4-dioxane" (p. 55).
    - 2017 BASF data: Why did EPA assign a score of 2 to "Sample Size," when the data set comprised only four data points from a single site?

v. Lack of dermal exposure data

EPA has no data on dermal exposures or dermal absorption in humans. Instead -- as the basis for its entire evaluation of dermal risks -- EPA heavily relies on Bronaugh, 1982 (see p. 76 for the first of many citations to this source), which apparently reported the results of an *in vitro* assay using excised human skin. This source is a chapter of a book, however, which has not been made available by EPA. It is not clear whether EPA itself has more than the book chapter, i.e., the original study. (EPA has not provided the source in response to a request for it EDF sent to

[22] U.S. EPA, *Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data* at pp. 124-25 (June 2019), https://www.epa.gov/sites/production/files/2019-06/documents/4_14-d_supplemental_-_data_quality_evaluation_environmental_release_and_occupational_exposure_06272019.pdf.

EPA on July 10.) It is also noteworthy that EPA did not subject this key data source to any systematic review.

EPA also relies on Marzulli et al., 1981, which examined absorption in adult rhesus monkeys. But the vehicles employed were methanol and skin lotion, and it is not clear how representative they are of absorption under the conditions of use in this risk evaluation. Moreover, the authors describe their results as providing only "crude estimates."

Further, EPA appears to have ignored relevant dermal absorption data. A 2013 study conducted by Dennerlein et al.[23] assessed the dermal absorption of three industrial chemicals, including 1-4 dioxane. The study found that 1,4 dioxane had the highest percutaneous penetration compared to the other two chemicals analyzed (anisole and cyclohexanone), with a penetration of 2,868.2 µg per 0.64 cm^2 of skin over four hours of exposure[24] and mean flux of 1,116.8–1,483.4 µg per cm^2 of skin per hour. It does not appear that EPA incorporated, or even evaluated, this study, as it cannot be found in either the Risk Evaluation or the Systematic Review Supplemental File.

EPA also argues that "only a fraction" of 1,4-dioxane on the skin will be absorbed due to its rapid evaporation (p. 75). To the extent this is the case, EPA does not appear to have accounted for the resulting inhalation exposure – or the potential for combined exposure pathways (see below - *Failure to consider combined exposure pathways for workers*) – to such a dermally exposed worker. Elsewhere in its draft, EPA notes that "if in aqueous solution, evaporation may be less likely" (p. 150).

In the absence of any actual monitoring data, EPA is forced to make other assumptions to estimate dose. For example, EPA assumes, without any explanation, that workers will experience only "one exposure event (applied dose) per work day" (p. 76).

All of these arguments remain speculative at best, however, given the dearth of actual data.

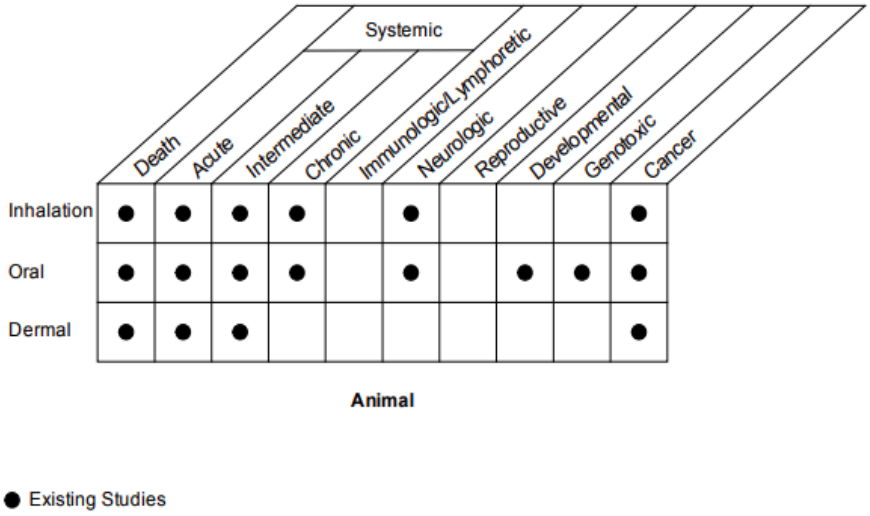
vi. Dearth of dermal toxicity data

EPA has identified no acute or repeated dose, short-term, subchronic, or chronic studies that examined toxicity via dermal exposure (pp. 85, 90). As a result it relied on extrapolation from oral and inhalation toxicity studies; we discuss in section 4.C of these comments the many concerns raised by this approach.

[23] Dennerlein, K. et al., Studies on percutaneous penetration of chemicals – Impact of storage conditions for excised human skin, *Toxicology in Vitro*, Volume 27, Issue 2, 2013, pp. 708-713.
[24] Bronaugh, 1982 used a 205-minute exposure, equivalent to 3.4 hours.

vii. Lack of reproductive/developmental/neurodevelopmental toxicity data

The only current available developmental toxicity study is Giavini et al 1985 (p. 87), which evaluated toxicity by the oral route of exposure. The figure below, from the 2012 ATSDR ToxProfile of 1,4-dioxane,[25] clearly shows the database deficiencies for reproductive & developmental endpoints through the inhalation & dermal routes. However, the Agency makes no effort to use its authority to fill these data gaps.



4. Analytic gaps/deficiencies

A. Environment

i. Misuse of TRI data

To conduct its analysis of aquatic water pathways, EPA relied on the 2015 Toxics Release Inventory (TRI) value for releases to water, which it asserted amounted to 35,402 lbs (pp. 46, 214). There are a number of flaws in EPA's approach.

First, EPA's use of the value reported in 2015 of 35,402 lbs as the amount of releases to water ignores indirect discharges of 1,4-dioxane to water. Total water releases in 2015, according to TRI, amounted to 56,935 lbs. According to EPA's Enforcement and Compliance History Online (ECHO) portal,[26] discharges to sewage treatment plants amounted to 24,815 lbs, which is the difference between the actual TRI value and that cited by EPA in the draft risk evaluation. EPA has provided no explanation for its decision to ignore the discharges to sewage treatment plants.

[25] Agency for Toxic Substances & Disease Registry, *Toxicological Profile for 1,4 Dioxane* at p. 139 (Apr. 2012), https://www.atsdr.cdc.gov/toxprofiles/tp187.pdf.
[26] *See* WATER POLLUTION SEARCH, https://echo.epa.gov/trends/loading-tool/water-pollution-search/ (last visited Jul. 19, 2019).

It may be that EPA's decision was based on its expectation that such discharges include 1,4-dioxane that was present as a byproduct (e.g., household discharges containing the chemical from the use of cleaning products, etc.), which it has decided to exclude from this risk evaluation. (See section 2.A of these comments for a discussion of the serious concerns that exclusion raises.) However, excluding all indirect discharges would also exclude *industrial* discharges to sewage treatment plants that contain 1,4-dioxane that had been intentionally produced. As EPA has acknowledged, sewage treatment results in only low rates of removal of 1,4-dioxane (p. 45).

Second, EPA relied on outdated TRI data, choosing to use data from 2015 even though data from 2016 and 2017 are readily available. EPA provided a cursory explanation for why it rejected use of the more recent updated data: "[i]t is not expected that the incorporation of the more recent TRI reporting years would have altered the conclusions of the screening-level assessment" (p. 213). However, the releases to water of 1,4-dioxane reported in 2015 (56,935 lbs) are significantly lower than the 2016 and 2017 reported releases, which are 222,991 lbs and 236,508 lbs respectively. As a result, EPA's analysis seriously underestimates the impacts from water releases of this chemical. Additionally, EPA's use of outdated environmental data is contrary to TSCA's mandates to take into consideration all reasonably available information, "including exposure information," (TSCA section 26(k)) and to use the best available science (TSCA section 26(h)).

ii. Failure to consider air and land releases reported under TRI and NEI

EPA has also ignored the impact on the environment of air and land releases of 1,4-dioxane. These releases are substantial. In 2015, companies reported discharging 62,596 pounds to air and 577,400 pounds to land of 1,4-dioxane under the TRI.

While EPA included the 2015 TRI data in a table in Appendix E, (p. 214), it conducted no evaluation of these environmental exposures in this risk evaluation, effectively treating them as equal to zero.

EPA also failed to cite and evaluate the air emission values reported for 1,4-dioxane through the National Emissions Inventory (NEI), which are much higher than those reported under the TRI: 134,484 lbs.[27]

iii. Failure to consider biosolids

In a cursory analysis of exposure via biosolids, EPA determined that "the exposures to surface water from biosolids are estimated to be low" (p. 131, 212). EPA also assumed, with no

[27] 2014 NATIONAL EMISSIONS INVENTORY (NEI) DATA, https://www.epa.gov/air-emissions-inventories/2014-national-emissions-inventory-nei-data (last visited Jul. 18, 2019).

explanation, that 1,4-dioxane "is not likely to accumulate in wastewater biosolids ***" (p. 45). These assertions are contradicted by publicly available data that demonstrate 1,4-dioxane is present in biosolids, and that the levels are not low. An analysis conducted by Policy Watch found that 1,4-dioxane was present in sludge from a manufacturing facility in Fayetteville, NC at a concentration of 20,400 ug/kg.[28] In a follow-up analysis by the North Carolina Department of Environmental Quality, sludge samples contained levels of 1,4-dioxane as high as 138,000 ug/kg.[29] Both analyses were conducted on samples from a facility that manufactures plastics, a condition of use of 1,4-dioxane (p. 30).

EPA's dismissal of exposures to 1,4-dioxane in biosolids is especially alarming in light of the findings in a recent Office of Inspector General report that indicates EPA "lacks the data or risk assessment tools" to make determinations on the risk levels for pollutants found in biosolids.[30] Moreover, according to OIG, "[t]he regulations for biosolids do not require the EPA to obtain the data necessary to complete risk assessments."[31] With little known about the pollutants in biosolids, how is EPA's statement that "1,4-dioxane is not likely to accumulate in wastewater biosolids" supported by the best available science?

iv. Failure to analyze exposures during distribution

EPA has conducted no analysis of releases or exposures occurring during distribution of 1,4-dioane or products containing it, based on the unsupported assertion that "chemicals are packaged in closed-system containers during distribution in commerce and no exposures are expected" (pp. 28, 165).

In the problem formulation, EPA took a similar approach, stating: "During distribution, 1,4-dioxane is contained in closed systems (e.g. drums, pails, bottles) so *releases and exposures are not expected*" (p. 37, emphasis added). This blanket assertion too was made with absolutely no supporting analysis or data, either documenting the extent to which the identified "closed systems" are actually used, or the extent to which they are in fact "closed" and lead to no

[28] Lisa Sorg, *PW special report: Unregulated, untested and unknown*, POLICY WATCH (Apr. 26, 2019), http://www.ncpolicywatch.com/2019/04/25/pw-special-report-unregulated-untested-and-unknown/; *see also*

[29] Letter from Taylor Cannon, GEL Laboratories, LLC, to Mark Brantley, NC Dept Environmental Quality (Mar. 21, 2019) (providing the analytical results for samples taken from DAK Americas) (copy of the letter is with EDF).

[30] U.S. OIG, *EPA Unable to Assess the Impact of Hundreds of Unregulated Pollutants in Land-Applied Biosolids on Human Health & the Environment* (2018), https://www.epa.gov/sites/production/files/2018-11/documents/_epaoig_20181115-19-p-0002.pdf.

[31] *Id.*

releases or exposures whatsoever, as EPA asserts. Even on their face, the examples raise many questions. For example: Are drums or bottles never open? How is a pail a "closed system"?

To the extent EPA relies on Department of Transportation (DOT) regulations to avoid analyzing exposures to 1,4-dioxane during distribution, any assumption that risks from those exposures are "adequately managed" is unfounded. While EPA refers to the DOT regulations at 49 C.F.R. § 171-177, EPA has made no attempt to explain or apparently even to discern what types of risks those regulations are intended to address, e.g., acute risks from emergency spills or risks from more routine, long-term exposures of workers engaged in distribution-related activities such as loading, unloading.

Those regulations were adopted pursuant to a mandate in the Hazardous Materials Transportation Act (HMTA) that DOT "prescribe regulations for the *safe* transportation, including security, of hazardous material in intrastate, interstate, and foreign commerce." 49 U.S.C. § 5103(b)(1) (emphasis added). What it means to provide "safe transportation" is not defined in the statute, nor in the rules adopted by DOT. EPA has made no effort to demonstrate whether and if so, how, it has determined the regulations are protecting workers from unreasonable risk during distribution. Notably, the Material Transportation Bureau (MTB), in adopting the regulations, stated that the rules were adopted "primarily to ensure that hazardous wastes are properly identified to carriers and that they are delivered to predetermined designated facilities." 45 Fed. Reg. 34,560, 34,569 (May 22, 1980) (emphasis added).

v. Reliance on qualitative and screening-level environmental assessments

EPA has acknowledged that its evaluation of environmental exposures and risks is based only on a "qualitative assessment of the physical-chemical properties and fate of 1,4-dioxane in the environment for sediment and land-applied biosolids" (p. 20) and a screening-level assessment of risks to aquatic organisms (p. 148). These are terms EPA has developed to seek to justify conducting assessments in the absence of sufficient information on hazards, exposures and risks of 1,4-dioxane. These terms have no basis in TSCA itself, which requires EPA to conduct robust risk evaluations of chemicals that are based on the "best available science" (TSCA section 26(h)) and all "reasonably available information" on hazards and exposures (TSCA section 26(k)), the latter defined by EPA in its Risk Evaluation Rule as encompassing "information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations."[32]

B. Human health

i. Inconsistencies with agency guidelines

In several instances, EPA inappropriately dismisses key data relevant to genotoxicity. For example, when discussing the Itoh and Hattori (2019) publication, EPA reports that the authors

[32] 40 C.F.R. § 702.33.

discounted the statistically significant increase in micronucleated immature erythrocytes (MNIE) because these changes were within the historical control range. However, this decision contradicts EPA Cancer Guidelines,[33] which states that:

> the standard for determining statistical significance of tumor incidence comes from a comparison of tumors in dosed animals with those in concurrent control animals…Generally speaking, statistically significant increases in tumor should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in concurrent controls are somewhat lower than average.

EPA's Benchmark Dose Guidance[34] also provides relevant commentary:

> Typically, all endpoints within a study that a risk assessor has judged to be relevant to the exposure should be considered from modeling. This will help ensure that no endpoints with the potential of having the most sensitive effect for risk assessment applications, usually having the lowest BMDL, are excluded from the analysis.

EPA also downplays its own cancer risk assessment guidance regarding when a linear no-threshold model should be used: "In the absence of other information about MOA, *EPA often takes* the health protective approach of assuming a linear no-threshold risk model consistent with a mutagenic mode of action" (p. 98, emphasis added). This approach is inconsistent with the Agency's cancer guidelines, which direct the agency to use the default linear approach in the absence of an alternative known MOA. Only when "alternative approaches have significant biological support" should an "assessment...present results using alternative approaches."[35] By contrast, in this risk evaluation, EPA continues to develop and present the threshold non-linear model in tandem with the default linear no-threshold model despite the scientific consensus otherwise that there is insufficient evidence to support the ~~non-~~threshold approach.[36]

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[33] U.S. EPA, *Guidelines for Carcinogen Risk Assessment* at pp. 2-20-2-21 (Mar. 20015), https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

[34] U.S. EPA, *Benchmark Dose Technical Guidance* at pp. 14-15 (June 2012), https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf.

[35] U.S. EPA, Guidelines for Carcinogen Risk Assessment at p. 1-15 (Mar. 20015), https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

[36] *See, e.g.*, Mich. Dep't of Envtl. Quality, Toxics Steering Group, 1,4-Dioxane Subcomm., Review of a 1,4-Dioxane Presentation by Michael Dourson, Ph.D. on October 8, 2013 (Feb. 2015), https://www.michigan.gov/documents/deq/deq-aqd-toxics-14-DioxaneTSG_Report_2015_487415_7.pdf; N.J. Dep't of Envtl. Protection, Response to Public Input on Draft Interim Ground Water Quality Criteria and Draft Interim Practical Quantitation Levels for Eleven Chemicals at pp. 11-17, https://www.state.nj.us/dep/dsr/supportdocs/11-

ii. Failure to consider combined exposure pathways for workers

EPA never bothers to add up its calculated risks from the inhalation and dermal exposures it does consider -- even though many workers could readily experience exposures by both routes, including over the same time period. EPA has acknowledged that dermal exposure results in systemic distribution of 1,4-dioxane (p. 90) just as do inhalation (and oral) exposures.

Furthermore, EPA never acknowledges the potential for simultaneous inhalation and dermal exposure. In the context of estimating dermal exposure, the agency states that "only a fraction of 1,4 dioxane that contacts the skin will be absorbed as the chemical readily evaporates from the skin" (p. 75). Despite acknowledging the likelihood of evaporation, which would lead to increased concentration in the air in the immediate vicinity of the dermally exposed worker, EPA never considers the potential risk of combined exposures through both inhalation and dermal routes. This also means EPA ignores the potential for synergistic effects in scenarios with combined inhalation and oral exposures, a finding of Take et al. (2012) that EPA only briefly mentions elsewhere in the draft (p. 84).

In addition, by ignoring *all* oral exposures to workers (p. 19; also problem formulation, p. 31), EPA is ignoring oral exposures arising from non-occupational sources. As a result, EPA fails even to consider the potential that such exposures, in conjunction with workplace inhalation exposures, could interact synergistically to increase systemic concentrations of 1,-4-dioxane, as observed by Take et al. (2012).

C. Dermal risk

For both the oral to dermal and inhalation to dermal extrapolations, EPA relies on the Bronaugh (1982) *in vitro* dermal absorption study to estimate dermal absorption. As highlighted earlier in our comments (section 3.B.v), this study is not publicly available and has not been subject to any quality review. Nevertheless, the Agency uses it in the calculation of applied human equivalent doses (HEDs), which are themselves used as a basis for reducing the interspecies uncertainty value from 10 to 3 (pp. 111, 118).

EPA has paid scant attention to the uncertainties that route-to-route extrapolations introduce. The source EPA cites for its approach to extrapolation (p. 150, citing USEPA 2004) recommends that, at a minimum, a thorough discussion of associated uncertainties be included when such extrapolation is used. As noted below, other authors have argued that an additional uncertainty

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chemicals-response.pdf; U.S. EPA, IRIS, *Toxicological Review of 1,4-Dioxane (With Inhalation Update)* at p. 137 (Sept. 2013), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf.

factor, or an increase in the uncertainty factor for database insufficiencies, may be warranted.[37] In this case, EPA has done neither.

i. Oral to dermal extrapolation

EDF has already discussed our serious concerns with EPA's dismissal of the liver tumors observed in female mice in the key oral cancer study it uses to extrapolate dermal cancer risks (see section 1.E.ii above).

EPA relied on oral-to-dermal extrapolation (p. 90) for sub-chronic/chronic non-cancer outcomes, with little acknowledgment of the substantial uncertainties associated with route-to-route extrapolation. The very guidance that EPA cites for its extrapolation protocol explicitly indicates the need for a thorough evaluation of uncertainty, including "a qualitative evaluation of key exposure variables and models, and their impact on the outcome."[38] Yet in this risk evaluation, EPA has provided only a single statement of uncertainty -- "oral to dermal route-to-route extrapolation assumes that the oral route of exposure is most relevant to dermal exposures" (p. 150) – which is far from sufficient. Some prior research even suggests the inclusion of additional UF for route-to-route extrapolation may be appropriate.[39]

ii. Inhalation to dermal extrapolation

EPA appears to use inappropriate model inputs for the chronic non-cancer assessment for dermal exposures extrapolated from chronic inhalation studies (p. 117): The agency uses an inhalation rate of 1.25 m^3/hr for their inhalation to dermal conversion. This does not match with the number in the EPA Exposure Factors Handbook[40] for average adult moderate activity level (Table 6-28 suggests 2.1 m^3/hr). EPA should explain the rationale for this deviation.

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[37] *See, e.g.*, Schröder, K., et al., *Evaluation of route-to-route extrapolation factors based on assessment of repeated dose toxicity studies compiled in the database RepDose®*, 261 TOXICOLOGY LETTERS 32-40 (Nov. 2016), https://www.ncbi.nlm.nih.gov/pubmed/27553675; Dankovic, D.A., et al., *The scientific basis of uncertainty factors used in setting occupational exposure limits*, 12 J. OF OCCUPATIONAL & ENVTL. HYGIENE 55-68 (Nov. 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4643360/.

[38] U.S. EPA, *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment)* at sec. 5-2 (June 2004), https://www.epa.gov/sites/production/files/2015-09/documents/part_e_final_revision_10-03-07.pdf.

[39] Schröder, K., et al., *Evaluation of route-to-route extrapolation factors based on assessment of repeated dose toxicity studies compiled in the database RepDose®*, 261 TOXICOLOGY LETTERS 32-40 (Nov. 2016), https://www.ncbi.nlm.nih.gov/pubmed/27553675.

[40] U.S. EPA, *Exposure Factors Handbook: 2011 Edition* (2011), http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=522996.

D. Inhalation risk

The Agency provides insufficient and/or irrelevant details for the chronic non-cancer inhalation risk estimates, obfuscating the modeling process. For example, in the discussion of Risk Characterization Assumptions and Uncertainties (p.150), EPA states that the "LOAEC was used with an uncertainty factor for LOAEC to NOAEC extrapolation." However, where and how it did so is not explained clearly in earlier sections of the document (ex: Section 4.2.6.2.3, pp. 111-114), where text and tabular calculations are provided for this outcome. Why EPA included this text about the LOAEC to NOAEC extrapolation within the discussion of Risk Characterization Assumptions and Uncertainties (p. 150) is also unclear, given that EPA ultimately used BMD in these calculations. As such, the Agency should have instead or also provided a discussion of assumptions and uncertainties relevant to BMD.

On page 135, EPA claims that an APF=10 respirator is sufficient to eliminate even high-end inhalation non-cancer risk "during industrial use." This is not accurate: EPA found that an APF=25 respirator is necessary to get the acute high-end MOE above the benchmark MOE (Table 5-4) and that even an APF=50 respirator is not sufficient to get the chronic high-end MOE above the benchmark MOE (Table 5-5). (The chronic finding is more accurately stated on p. 137.)

For the evaluation of acute/short term inhalation effects, EPA uses Mattie et al 2012 to derive PODs for liver effects (which were assumed to be protective of acute effects to the nasal system, lungs, and brain). While this study is more recent than (and was not yet available) when ATSDR completed its ToxProfile in 2012, the study was conducted in rats. By contrast, ATSDR cited Ernstgard et al., 2006, which was conducted in humans and evaluated eye and respiratory irritation as well as pulmonary function. Importantly, this study does not require interspecies extrapolation. EPA's decision to utilize the Mattie et al. 2012 study results in a much higher POD(HEC), yet their decision not to utilize the Ernstgard et al., 2006 study is not well justified. EPA merely states that "there were limitations with the human studies [ex: Ernstgard et al. 2006] that precluded their use for quantitative risk assessment, including for example, the absence of measures of systemic effects" (p. 87); no assessment of data quality is presented to support this dismissal.

5. Risk characterizations

Despite EPA's indications to the contrary and the numerous data gaps and deficiencies in its analysis identified above, EPA has found numerous, significant risks to workers. Summaries of these findings are provided below.

A. Inhalation risks

Acute (Table 5-4, p. 136):

- For 8 of 11 conditions of use (COUs), high-end MOEs are below EPA's benchmark MOE (300) and respirators are required to get above the benchmark (a respirator with an APF=50 is required for 2 COUs; APF=25 for 1 COU; APF=10 for 5 COUs).
- For 5 of 11 COUs, central tendency MOEs are below the benchmark MOE and respirators are required to get above the benchmark (APF=25 for 2 COUs; APF=10 for 3 COUs).

Chronic non-cancer (Table 5-5, p. 137):

- For 8 of 10 COUs, ***both central tendency and high-end MOEs are below the benchmark MOE (30)***.
    - For 5 of these, even an APF=50 isn't sufficient to get the high-end MOE above the benchmark.
    - For the other 3 COUs, respirators are required to get the high-end MOE above the benchmark (APF=50 for 1 COU; APF=10 for 2 COUs).
- For 1 of these, even an APF=50 isn't sufficient to get the central tendency MOE above the benchmark. For the other 7 COUs, respirators are required to get the central tendency MOE above the benchmark (APF=50 for 1 COU; APF=25 for 1 COU; APF=10 for 5 COUs).

Cancer (Table 5-7, p. 140):

- ***For all 10 COUs, inhalation cancer risk levels for workers are above 1 in 100,000 – even with respirator use – for both central tendency and high-end exposures***. Even for ONUs, the same is true for film cement use (Table 5-8, p. 141).
- For 7 of the 10 COUs, high-end cancer risk levels for workers are above 1 in 10,000.
    - For 1 of these, even an APF=50 isn't sufficient to get the high-end cancer risk below this risk level.
    - For the other 6 COUs, respirators are necessary to get the high-end cancer risk levels below 1 in 10,000 (APF=50 for 2 COUs; APF=25 for 3 COUs; APF=10 for 1 COU).
- For 5 of 10 COUs, central tendency cancer risk levels are also above 1 in 10,000. For these, respirators are necessary to get the central tendency cancer risks risk levels below 1 in 10,000 (APF=25 for 1 COU; APF=10 for 4 COUs).

B. Dermal risks[41]

Acute (Table 5-9, p. 142):

- For 8 of 10 COUs, high-end MOEs are below the benchmark MOE (300) and gloves with a protection factor of 5 (PF=5) are required to get above the benchmark.
- For 4 of the 10 COUs, central tendency MOEs are below the benchmark MOE (based on the text just above the table; EPA has not provided the specific data for these exposures or what gloves are necessary to get above the benchmark).

Chronic non-cancer (Table 5-10, p. 144 – EPA doesn't distinguish between high-end and central tendency exposures):

- For 9 of 11 COUs, the MOEs are below the benchmark MOE (30).
    - For 5 of these, even PF=5 gloves aren't sufficient to get above the benchmark.
    - For the other 4 COUs, PF=5 gloves are required to get above the benchmark.

Cancer (Table 5-11, p. 145 – EPA doesn't distinguish between high-end and central tendency exposures):

- ***For 9 of 11 COUs, dermal cancer risk levels for workers are above 1 in 100,000 – even with PF=20 glove use***.
- ***For 9 of 11 COUs, dermal cancer risk levels for workers are above 1 in 10,000 – even with PF=5 glove use***.
    - For 8 of these, PF=10 gloves still leave risk above 1 in 10,000, and
    - For 6 of these, even PF=20 gloves are not sufficient to get risk below 1 in 10,000.

C. Aggregate vs. sentinel exposures

EPA provides no significant discussion of its decision to rely on sentinel exposures instead of aggregate exposures, and EPA provides no support for the decision to consider the highest exposure to be sentinel (vs. the exposure of the longest duration/frequency, etc.) (p. 152). Nor does EPA provide any rationale for how its decision to conduct a sentinel exposure assessment comports with its collapsing of multiple uses and scenarios into single scenarios (see section 2.C of these comments): On what basis did EPA determine that its selected scenario is representative

[41] The tables presenting the dermal data need revision for accuracy and clarification:

- Table 5-9:
    - Columns showing the results for central tendency scenarios need to be added.
    - The values in the PF=5 column that are <3400 need to be boldfaced
- Tables 5-10 and 5-11: Columns showing the results for central tendency as well as high-end scenarios need to be added.

of all of the scenarios that were collapsed into it? And that exposures for that scenario were in fact the most significant? EPA has provided no such analysis in its draft risk evaluation.

6. Flaws in EPA's unreasonable risk definition and determinations

A. Expectation of compliance with existing laws and standards

In reaching its unreasonable risks determinations, "EPA expects there is compliance with all federal and state laws, such as worker protection standards, unless case-specific facts indicate otherwise" (p. 175, FN 1). EPA goes on to conclude that "therefore existing OSHA regulations for worker protection and hazard communication will result in use of appropriate PPE consistent with the applicable SDSs in a manner adequate to protect workers." As noted above, EPA mischaracterizes these OSHA regulations, which do *not* in fact require that persons comply with SDSs.

It is wholly inappropriate for EPA to simply assume either that there is universal compliance with laws and recommended standards, or that even when complied with, such requirements eliminate all risk such that EPA can ignore the contribution of such regulated activities to the overall risks posed by 1,4-dioxane. EPA has provided no analysis whatsoever of the degree of compliance with various requirements, including the extent to which they are effectively enforced. It has made no attempt to identify, let alone evaluate, the risks posed by the releases and exposures that continue to occur even in the presence of those requirements, and their contribution to the total exposure and risks. EPA has also failed to acknowledge that the other requirements derive from statutes that establish different criteria for establishing requirements to address human and environmental health risks. Many of these other statutes, for example, require EPA or other agencies to consider factors such as cost and feasibility when setting standards -- factors that TSCA explicitly forbids EPA from taking into account when assessing risks. TSCA section 6(b)(4)(A) states (emphasis added):

> The Administrator shall conduct risk evaluations pursuant to this paragraph to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, *without consideration of costs or other nonrisk factors*, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use.

B. Allowance for exceedances for high-end risks when finding no unreasonable risk

EPA states that its "determination of unreasonable risk is likely to consider the risk estimates associated with the *central tendency exposure scenarios*" (p. 151, emphasis added). EPA also states (p. 152, emphasis added):

> Where risks greater than the acceptable benchmarks are identified for high-end exposures, but *not for central tendency exposures*, and where EPA determines that a potentially exposed or susceptible subpopulation is not expected to be affected under the conditions of use, EPA may determine that while some risk exists, the risk is not unreasonable for the occupational conditions of use.

This is not theoretical: EPA has applied this approach to specific risk determinations in this risk evaluation; for examples, see pp. 160, 161.

Among other concerns, EPA's approach is at odds with its obligation under TSCA to conduct risk evaluations that ensure protection of "potentially exposed or susceptible subpopulations," which TSCA explicitly defines as including workers. Elsewhere, EPA represents its high-end estimates as "generally intended to cover the *most exposed* individuals or sub-populations," while its central tendency estimates apply to the "average or typical exposure" that workers experience (p. 153). But TSCA does not allow EPA to protect only the "average or typically exposed" workers; in fact, when it comes to workers EPA is required to protect all of them.

Moreover, EPA committed to using sentinel exposure levels which it defines as "the exposure to a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures" (p. 152). How can EPA justify relying on the central tendency over the high-end exposure scenario when EPA has committed to using the "plausible upper bound of exposure" in its exposure assessments?

C. 1 in 10,000 cancer risk level deemed reasonable for workers

EPA has relied on NIOSH guidance in order to establish 1 x 10-4 as the cancer risk benchmark for workers (pp. 133, 153, 155). EPA cites the *Benzene* decision for support (p. 155, footnote 12), but that case pertained to how the standard for protection applied under OSHA was to be determined, not under TSCA. EPA's decision is wholly at odds with its own acknowledgment two pages earlier that other laws have standards that differ from TSCA's (p. 153, footnote 10).

EPA is required to protect workers, both generally and as a "potentially exposed or susceptible subpopulation," under TSCA, not under OSHA. The 2016 amendments to TSCA strengthened EPA's already-existing mandate to protect workers. TSCA's new definition of "potentially exposed or susceptible subpopulation" has no asterisk next to workers, and there is no basis in TSCA for EPA to provide less protection to workers than any other such subpopulation, let alone than the general population. Yet that is exactly what EPA has done here.

The 2016 amendments to TSCA also explicitly preclude EPA from considering feasibility or other non-risk factors when determining whether a chemical presents an "unreasonable risk," including to workers; see TSCA section 6(b)(4)(A). Yet EPA invokes standards under other

statutes that lack this prohibition in an effort to claim precedent for its 1 x 10-4 benchmark (p. 155, footnote 11).

Moreover, in implementing TSCA (even before the amendments) and its other environmental statutes, EPA has generally sought to reduce population risks from chemicals in commerce that are carcinogens to below about one case per one million people. See, for example, this EPA statement from 1989: "EPA believes *** that it should reduce risks to less than 1 x 10-6 for as many exposed people as reasonably possible." National Emission Standards for Hazardous Air Pollutants; Radionuclides, 54 Fed. Reg. 51,654, 51,686 (Dec. 15, 1989).

In grasping for support for its approach in this risk evaluation by citing other mentions by EPA of the 1 x 10-4 risk level (p. 155, footnote 11), EPA blurs a critical distinction made when EPA has invoked the less stringent level of protection from cancer risks: the level set to reflect the maximum risk faced by any individual vs. the level set to protect a broader population. EPA invokes the "two-step approach" used under the Clean Air Act, where EPA includes a "limit on *maximum individual* lifetime [cancer] risk (MIR) of approximately 1 in 10 thousand" (p. 155 n. 11, citing 54 Fed. Reg. 38,045 (Sept. 14, 1989)) (emphasis added). But that is entirely different than the level set to protect the vast majority of the population in question.

More specifically, the two-step, risk-based decision framework for the National Emission Standard for Hazardous Air Pollutants (NESHAP) program is described as follows by EPA:

> First, the rule sets an upper limit of acceptable risk at about a 1-in-10,000 (or 100-in-1 million) lifetime cancer risk for the *most exposed person*. As the rule explains, "The EPA will generally presume that if the risk to that individual [the Maximum Individual Risk] is no higher than approximately 1 in 10 thousand, that risk level is considered acceptable and EPA then considers the other health and risk factors to complete an overall judgment on acceptability."
>
> Second, the benzene rule set a target of protecting the *most people possible* to an individual lifetime risk level no higher than about *1-in-1 million*.[42]

But in this risk evaluation, EPA has set a risk level for the entire worker population that is the same as the level EPA elsewhere set for the most exposed individual in a population.

EPA then erroneously invokes this level repeatedly to find the majority of conditions of use of 1,4-dioxane to pose no risk to *any* workers, thereby subjecting many tens of thousands of workers to cancer risks that are as much as *two orders of magnitude higher* than warranted. This approach must be rejected on scientific as well as legal grounds.

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[42] WHAT DOES EPA BELIEVE CONSTITUTES AN ACCEPTABLE LEVEL OF RISK?, https://www.epa.gov/national-air-toxics-assessment/nata-frequent-questions#risk2 (emphasis added) (last visited Jul. 19, 2019).

D. Shifting the goalposts when risk values are only a little above acceptable benchmarks

EPA has instituted an approach under which it can still deem a risk to be reasonable even though it exceeds the applicable acceptable level, as long as it is "close" to the acceptable level. Specifically, EPA states that it can consider "the proximity of the calculated risk estimate to the benchmark to determine that this condition of use does not present an unreasonable risk" (p. 169). Indeed, EPA had applied this approach to multiple conditions of use (pp. 159-60, 160-61, 169). In these cases EPA found its estimated MOEs of 25 or 17, well below its benchmark MOE of 30, still do not constitute unreasonable risks because they are in "proximity" to the benchmark.

But EPA applies this in only one direction in the risk evaluation. Even where EPA's estimated MOEs are only slightly greater than the benchmark MOE, EPA still finds no unreasonable risk. See, for example:

- Table 5-5, rightmost column for Film Cement: calculated MOE of 31 vs benchmark MOE of 30 is deemed not to represent unreasonable risk.
- Table 5-4, rightmost column for Industrial Use: calculated MOE of 338 vs benchmark MOE of 300 is deemed not to represent unreasonable risk.

E. Misleading characterizations of EPA's dermal exposure and risk analysis in its risk determinations

EPA repeatedly states in the Risk Determination section that the agency's approach to estimating dermal exposures "could overestimate risk." EPA states: "EPA chose to use 3.2%, the higher value, for the dermal absorption factor. The actual absorption could be ten-fold lower based on the Bronaugh *in vitro* study (Bronaugh, 1982).[43] For this pathway, EPA expects that the risks are not underestimated." (For examples of this language, see pp. 158, 163).

EPA's *actual* analysis of what absorption values and assumptions were applied to which scenarios is far from clear and at the very least must be far more thoroughly explained. Based on our best effort to discern what EPA did, it appears the description just cited mischaracterizes EPA's actual analysis, which cannot be fairly characterized as an overestimation of exposure, for several reasons:

1. EPA states that it used the higher 3.2% absorption rate *only* in occluded scenarios, where gloves are worn: "[f]or quantifying potential dermal risks to workers, EPA used the

[43] As we noted in section 1.E.i of these comments, the Bronaugh 1982 study EPA refers to is not publicly available, so its details cannot be discerned.

measured absorption values of 0.3% for scenarios without gloves and 3.2% for scenarios with gloves to quantify the amount of the applied dermal dose that would be systemically available." (p. 76) This would be appropriate, and necessary, as Bronaugh, 1982 found, according to EPA, that "[d]ermal penetration of 1,4-dioxane was 3.2% of the applied dose for the occluded condition, and 0.3% for unoccluded" (p. 86).

However, it is not at all clear that EPA implemented this approach. Its risk values for the scenarios without gloves are reduced exactly by the protection factor (PF) EPA assumed for the three with-gloves scenarios. See Table 5-10 on p. 144 and Table 5-11 on p. 145. This should not be the case if EPA applied different values for skin absorption for the no-gloves and gloves scenarios.

2. If EPA *did* use the lower 0.3% for scenarios where gloves are not worn (which it does not state it did in the Risk Determination sections), then the more conservative approach would have been to also use the higher 3.2% absorption for the non-occluded/no-glove scenario. Support for this is provided by the other study EPA cites, Marzulli et al., 1981, which found a dermal absorption rate of 2-3% in a *non-occluded* scenario (albeit after a 24-hour exposure). While EPA described the study (p. 83), it appears not to have chosen to use this more conservative absorption rate for non-occluded/no glove scenarios based on the statement on p. 76 cited above.

3. Elsewhere in the draft, EPA notes some of the numerous ways in which glove use can actually *increase* skin exposure through occlusion (p. 292): "[g]loves can prevent the evaporation of volatile chemicals from the skin. Chemicals trapped in the glove may be broadly distributed over the skin (increasing S in Equation G-13), or if not distributed within the glove, the chemical mass concentration on the skin at the site of contamination may be maintained for prolonged periods of time."

   However, it is not clear whether, and if so, how EPA's analysis accounted for such factors that could lead to increased skin absorption during use of gloves.

4. EPA appears to want to have it both ways: To acknowledge the limitations of gloves and their potential to increase skin absorption, but then to simply assume that gloves actually provide 5x, 10x or 20x levels of protection over no gloves without citing any evidence to support these values.

This issue is clearly highly complex. EPA needs to provide a far more thorough analysis and explanation than it has provided. In doing so, it should also account for more recent data, such as Dennerlein et al., 2013 (see section 3.B.v in these comments for further detail).

Further, EPA only cites the risk estimates for the 20x PFs in the Risk Determination section, ignoring the higher risks found with no gloves or lower PFs. The premise seems to be that if the most protective gloves available reduce risk to below the benchmark, then there is no unreasonable risk. This approach will allow clear risks to occur whenever a worker uses

anything less than the most protective gloves (or no gloves), a scenario quite likely to occur in the real world.

7. Systematic review issues

A. OPPT does not provide explanation nor empirical support for its revisions to the systematic review data quality criteria for epidemiological studies, and certain revisions make it more difficult for epidemiological studies to be scored overall as high quality.

- OPPT released an updated version of its systematic review data quality criteria for epidemiological studies, but did not provide any explanation for the numerous changes it made to these criteria. OPPT's scoring methodology is already at odds with best practices in systematic review (see Section 4 of EDF's previous comments on this issue[44]), and the agency's decision to alter scoring criteria without providing any empirical rationale for the changes further underscores that the study quality evaluation strategy that OPPT developed is not evidence-based.
- At least six metrics in OPPT's updated epidemiological criteria can no longer receive a score of High. These changes preclude epidemiological studies from receiving High scores for all study metrics—this was previously possible. Notably, these types of revisions to the epi criteria—prohibiting a score of high for certain data quality metrics—did not occur for animal or in vitro studies where it is remains possible to score High across every data quality metric. The effect is to diminish the contribution of epidemiological evidence relative to animal and in vitro studies.
- There were four instances where professional judgment was used to up/downgrade the overall study quality scores for animal toxicity studies (see Supplemental File for Animal and In Vitro studies[45]). Importantly, the treatment of two of these studies (Kano 2008 and Argus 1965) highlights but one of many deeply flawed aspects of OPPT's systematic review methodology: if a single metric is assigned a score of Unacceptable the entire study is dismissed.

[44] Environmental Defense Fund Comments on Application of Systematic Review in TSCA Risk Evaluations, submitted August 16, 2018, available at https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0077.

[45] USEPA 2019, Risk Evaluation for 1,4-Dioxane, Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Animal and In Vitro Studies, available at https://www.epa.gov/sites/production/files/2019-06/documents/7_1-4-d_supplement_-_data_quality_evaluation_animal_and_in_vitro_tox_06272019.pdf.

B. OPPT's dermal absorption analyses rely heavily on a single study that is not publicly available and was not evaluated using the agency's systematic review process.

- Dermal absorption analyses in the draft risk evaluation for 1,4-dioxane hinge largely on what the agency refers to as the "Bronaugh in vitro study" (e.g., p. 110). This source (Bronaugh, 1982) does not appear to be publicly available. Moreover, the HERO page indicates that this "in vitro study" is in fact a book chapter rather than an actual scientific study document. The source is not in any of OPPT's supplemental files containing the systematic review data quality evaluation sheets. Thus, OPPT's entire characterization of a central human exposure consideration (dermal absorption) is drawn from a 1982 book chapter that is not publicly accessible, and for which there is no indication that an underlying study is available to assess through OPPT's systematic review approach.
- OPPT relies on Bronaugh 1982 to derive toxicity values for multiple types of dermal hazard:
    - Acute/short-term POD for dermal exposures – section 4.2.6.2.2, p. 110-111
    - Chronic non-cancer POD for dermal exposures – section 4.2.6.2.5, p. 117-118
    - Chronic cancer unit risk for dermal exposures – section 4.2.6.2.7, p. 122-123

C. OPPT has inappropriately scored an occupational exposure study Unacceptable, removing critical data from consideration in the risk evaluation.

- OPPT gave a score of unacceptable to a workplace monitoring study (OSHA, 2016); chemical exposure health data (p. 105 of SR Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data)
- Metric 3 (Applicability) has been scored Unacceptable, with the reviewer comment stating, "Looks like it should be an excel file with exposure data, but it's all smooshed together in a text file and not useful" (p. 105).
    - The explanation provided in the reviewer comment is absurd and inappropriately results in a score of Unacceptable. In OPPT's scoring guidelines for this study type (Application of SR in TSCA REs document, p. 76), the description for Unacceptable for the Applicability metric states, "The data are from an occupational or non-occupational scenario that does not apply to any occupational scenario within the scope of the risk evaluation." Thus, a study should only be given a score of Unacceptable for this metric when the data are not within the scope of the evaluation. That is not the case here.

- To the extent OPPT had trouble accessing the data in a useable form, OPPT should have worked with OSHA to obtain the data, e.g., in an Excel sheet. The information is reasonably available and should have been considered by EPA in its analysis.

D. OPPT has again failed to define and explain its approach to evidence integration. Further, the approach taken to evidence integration in the draft 1,4-dioxane risk evaluation does not align with best practices as reflected and shared by leading systematic review methods for chemical assessment (e.g., OHAT, NavGuide, IRIS).

- As we have described in previous comments,[46] OPPT has not provided a pre-established methodology for its approach to evidence integration. This violates the agency's own definition of weight of the scientific evidence; the final rule *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* states that weight of the scientific evidence is:

> "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."

- Rather than providing a pre-established protocol for evidence integration, OPPT's approach to evidence integration appears to be limited to the development of a "weight-of-the-scientific evidence narrative" (p. 82). This type of narrative approach is explicitly frowned upon in systematic review -- historically producing assessments of evidence that were inconsistent and lacked transparency -- and in large part motivated the inception of systematic review.

* * * * *

EDF appreciates the opportunity to provide comments and EPA's consideration of them.

[46] Environmental Defense Fund Comments on Application of Systematic Review in TSCA Risk Evaluations, submitted August 16, 2018, available at https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0077; and Environmental Defense Fund Comments on Draft Risk Evaluation for C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline- 1,3,8,10(2H,9H)-tetrone), submitted January 14, 2019, available at https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0013.