



**Environmental Defense Fund  
Comments for Toxic Substances Control Act (TSCA)  
Science Advisory Committee on Chemicals Review of  
the Draft Risk Evaluation of Trichloroethylene  
Docket ID: EPA-HQ-OPPT-2019-0500**

**Submitted March 18, 2020**

Environmental Defense Fund (EDF) appreciates the opportunity to provide comments on the Environmental Protection Agency's (EPA) draft risk evaluation for trichloroethylene (TCE) being prepared under section 6(b)(4) of the Toxic Substances Control Act (TSCA) as amended by the Lautenberg Act, enacted on June 22, 2016.<sup>1</sup>

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 TCE. They have been prepared in the few weeks provided by EPA to submit comments for consideration by the SACC. EDF will also be providing oral comments at the SACC meeting scheduled for March 24-26, 2020. 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 April 27, 2020. We request that these comments be immediately provided to the SACC for its review and consideration.

**Summary**

In its draft risk evaluation for TCE, EPA has grossly understated the risks from exposure to the chemical. EPA did more frequently identify unreasonable risks than in draft risk evaluations for other chemicals released in the past year, making the deficiencies harder to discern. EPA has employed a host of unwarranted and unsupported assumptions and methodological approaches that lead it to either avoid identifying unreasonable risk when it should have, or to understate the extent and magnitude of the unreasonable risks it did identify. Below we summarize some of the major concerns addressed in these comments.

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<sup>1</sup> U.S. EPA, *Draft Risk Evaluation for Trichloroethylene CASRN: 79-01-6* (February 2020), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0500-0002>. Further citations in these comments of the draft risk evaluation consist of only a page number in parentheses.

Exclusion of known uses and exposures: Once again, EPA has abdicated its responsibility under TSCA to identify and evaluate the risks the chemical presents to the general population, by excluding from its risk evaluation conditions of use and exposures that are known or reasonably foreseen, including exposures from releases of TCE to air, water, and land. EPA has also failed to consider exposure to background levels of TCE. See section 2 of these comments.

Insufficient consideration of vulnerable subpopulations: EPA has not met its mandatory duty under TSCA to thoroughly identify and evaluate the risks to vulnerable subpopulations. These include, in addition to workers: subpopulations that are more susceptible to TCE exposure, including pregnant women and the developing fetus and diseased subpopulations including those managing kidney and liver disease; as well as consumers and others who may be at risk of cancer from acute exposures. See sections 1.A. and 4.A. of these comments.

Failure to protect against the most sensitive endpoint, fetal cardiac malformations: EPA's reliance on immune-related endpoints instead of fetal cardiac malformations for its determinations of acute and chronic risk deviates from scientific best practices, defies requirements under the law, ignores longstanding agency policy, and is not sufficiently protective of public health. See sections 4.C., D. and E. of these comments.

Underestimation of occupational risks: Of particular concern is the extent to which EPA has underestimated occupational risks. EDF has analyzed each of the individual risk estimates EPA has made in this draft risk evaluation, which is presented in sections 5.A. and 7.A. of these comments. EDF's analyses identify and quantify several major ways in which EPA has underestimated occupational risks, including through: EPA's unsupported assumptions regarding worker use of personal protective equipment in many scenarios; its use of a cancer risk level for workers that fails to protect them as a vulnerable subpopulation as required by TSCA; its failure to consider combined exposures of workers from multiple sources; and its failure to identify unreasonable risks for the most highly exposed (and hence especially vulnerable) occupational non-users (ONUs). EPA's exposure assessment has underestimated occupational exposures. See sections 5.A, 5.B., and 7.A. of these comments.

Dismissal of risk by invoking uncertainty: EPA invokes uncertainty as an unwarranted basis for ignoring risks it has identified to the environment and to ONUs, and for not accounting for combined exposures to TCE. See sections 5.B.i., 5.E.i., 7.A.iii., and 7.B. of these comments.

Failure to adequately evaluate environmental risks of TCE release and exposure: EPA has over-relied on predictions from physical-chemical properties and unwarranted assumptions to ignore or underestimate environmental risks, including to aquatic, sediment, and terrestrial organisms, EPA has also ignored available data on environmental releases. See section 6 of these comments.

Use of a flawed systematic review approach: EPA has continued to use its flawed TSCA systematic review approach that inappropriately downgrades epidemiological evidence, fails to provide and utilize a pre-established methodology for evidence integration, and selectively includes or excludes studies in a manner that reveals inconsistency and bias. See section 8 of these comments.

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.

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## 1. Broad/cross-cutting concerns

### A. EPA has given insufficient consideration to vulnerable subpopulations.

EPA has failed to sufficiently identify and address potential hazards, exposures, and risks to several vulnerable subpopulations. Our concerns are detailed in the following sections of these comments:

- Workers and ONUs: Sections 1.A., 1.B., 2.E., 5.A., 5.B., 5.C., 5.D., 7.A.
- Consumers: Sections 2.B., 2.D., 4.A., 5.B., 5.E.
- Pregnant women, infants and children: Sections 1.A.i., 4.A., 4.C.-E.
- Health-affected or genetically susceptible subpopulations: Section 1.A.
- People in proximity to conditions of use or sources of contamination: Sections 2.C., 2.D.

The remainder of this subsection identifies additional ways not discussed elsewhere in which EPA has given insufficient consideration to vulnerable subpopulations.

*i. Insufficient consideration of the unique susceptibility of pregnant women and the developing fetus*

*a. Dermal risk estimates do not account for women of childbearing age.*

On p. 352 of the draft risk evaluation, EPA states:

Dermal risk estimates were calculated for both average workers and women of childbearing age [Occupational Risk Estimate Calculator. Docket # EPA-HQ-OPPT-2019-0500], based on differences in delivered dose accounting for differing body weight and hand size. Exposures differ by only ~10% between these groups, so this difference is relatively insignificant considering the magnitude of risk estimates relative to the benchmark MOE. Accordingly, the risk characterization section only presents dermal risk estimates for average adult workers (Section 4.2.2).

Under TSCA, EPA has a mandate to protect vulnerable populations, including women of childbearing age. Thus, the Agency must use exposure values applicable to subpopulations with elevated exposure, even if EPA believes the values would not significantly affect the overall risk conclusion. To ignore these data is counter to the law by failing to identify the actual risks to potentially exposed or susceptible subpopulations; their omission also makes it more like EPA will fail to identify an unreasonable risk where it should have, and even where it identifies such a risk, will fail to adequately address that risk in subsection regulation under TSCA section 6. EPA's practice of choosing to ignore risks it deems "relatively insignificant" also fails to

consider the contribution of such risks to overall risks faced by individuals or subpopulations in light of additional exposures they experience.

*b. Insufficient acknowledgement of the importance of potential transfer through the blood-brain barrier*

EPA appropriately acknowledges that TCE can be found in many tissues including the brain (p. 203); however, EPA fails to explicitly highlight that TCE can readily cross the blood-brain barrier. For example, the 2019 ATSDR ToxProfile for TCE states: “Trichloroethylene crosses the blood-brain barrier, and the extent of transfer could possibly be greater in young children, although trichloroethylene is expected to readily cross the blood-brain barrier in all age groups.”<sup>2</sup> This is essential to emphasize given the evidence for neurotoxicity, including developmental neurotoxicity (see, for example, sections 3.2.3.1.3 and 3.2.3.1.6 of the draft risk evaluation).

*ii. Insufficient acknowledgment of variability in human susceptibility*

*a. Failure to highlight key groups of susceptible individuals*

In section 3.2.5.2, EPA acknowledges a wide variety of potentially exposed or susceptible subpopulations. In addition to those EPA lists, EPA should explicitly acknowledge the following additional groups that represent key susceptible subpopulations:<sup>3</sup>

- Individuals with compromised liver or kidney function. In the U.S. there are more than 4.5 million adults living with chronic liver disease<sup>4</sup> and more than 6 million adults with diagnosed kidney disease.<sup>5</sup>
- Individuals with cardiac arrhythmias. Between 3 and 6 million individuals in the U.S. have atrial fibrillation, the most common type of heart arrhythmia.<sup>6</sup>
- Individuals co-exposed to chemicals that interact with TCE metabolism, including:
  - Chlorinated hydrocarbons, which commonly co-occur in drinking water. According to the U.S. Geological Survey, chlorinated solvents are “one of the two most frequently detected VOC groups in the Nation’s aquifers”<sup>7</sup>

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<sup>2</sup> Agency for Toxic Substances and Disease Registry (ATSDR). 2019. Toxicological profile for Trichloroethylene (TCE). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. P. 261.

<sup>3</sup> Ibid, p. 271.

<sup>4</sup> <https://www.cdc.gov/nchs/fastats/liver-disease.htm>.

<sup>5</sup> <https://www.cdc.gov/nchs/fastats/kidney-disease.htm>.

<sup>6</sup> [https://www.cdc.gov/heartdisease/atrial\\_fibrillation.htm](https://www.cdc.gov/heartdisease/atrial_fibrillation.htm).

<sup>7</sup> Zogorski, John S. *The quality of our nation's waters: Volatile organic compounds in the nation's ground water and drinking-water supply wells*. Vol. 1292. Geological Survey (USGS), 2006.

- Phenobarbital, a medication used to treat epilepsy. In the U.S., there are more than 3 million adults with epilepsy.<sup>8</sup>

*b. Lack of detail regarding the extent of genetic variation in key metabolic pathways*

EPA appropriately acknowledges that “[s]ignificant variability may exist in human susceptibility to TCE toxicity given the existence of CYP isoforms and the variability in CYP-mediated TCE oxidation” (p. 204). Yet, given the implications of this variability for considering risks to potentially exposed or susceptible subpopulations, further information on and analysis of the potential variability in CYP oxidation across the human population should be provided. For example, in the 2019 ATSDR ToxProfile, that Agency clearly stated that “human variability in metabolism of trichloroethylene via cytochrome P450-dependent pathways was within a 10-fold range.”<sup>9</sup> Such quantitative details are crucial for understanding the true impact of these variations.

*iii. Failure to consider workers with compromised health*

EPA’s Risk Estimation Approach for Human Health Risk only considers *healthy* female and male workers (see footnote 1, Table 4-4, p. 277). Assuming that all workers are “healthy” is erroneous and counter to the mandate of TSCA, which directs EPA to protect the most vulnerable subpopulations.

*iv. Insufficient consideration of potential elevated respiration rates in exposed workers*

On p. 352 of the draft risk evaluation, the Agency states:

EPA expects that variability in human physiological factors (e.g., breathing rate, body weight, tidal volume [sic]) which may affect internal delivered concentration or dose is sufficiently accounted for in the PBPK model, although some differences among lifestyles or between working and at-rest individuals may not have been accounted for. The use of HEC/HED99 values is expected to account for the vast majority of physiological differences among individuals.”

Based on this paragraph, it is unclear whether the PBPK model sufficiently addresses potential elevated respiratory rates in workers. EPA states that it “expects” its model has accounted for variability in basic “physiological factors (e.g. breathing rate)” but also that “some differences... between working and at-rest individuals may not have been accounted for.” Workers are a

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<sup>8</sup> <https://www.cdc.gov/epilepsy/data/index.html>.

<sup>9</sup> Agency for Toxic Substances and Disease Registry (ATSDR). 2019. Toxicological profile for Trichloroethylene (TCE). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. P. 207.

crucial vulnerable subpopulation with respect to TCE, and therefore EPA must fully and accurately characterize and account for potential elevated respiratory rates among active workers.

In the recent National Academies of Sciences, Engineering, and Medicine (NASEM) *Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene*, the NAS highlights a similar concern:<sup>10</sup>

Lastly, all PBPK-based derivations of HECs were performed using resting ventilation and associated cardiac output physiological profiles. This may be appropriate for clerical or other office workers (e.g., vapor intrusion within an office building) but for other DOD occupations where ventilation and cardiac output are elevated by more strenuous exertion for extended durations, the resulting HECs may not be sufficiently protective. If such workplace exposure cases are considered relevant to DOD, the committee recommends incorporating exercise (work) physiology and realistic durations from actual job profiles into PBPK simulations for selected end points most likely to drive the OEL.

In the draft risk evaluation, EPA is clearly charged with examining the risks to workers in addition to clerical or other office workers. If EPA did use resting cardiac profiles, this analysis must be enhanced to provide more realistic estimates of exposure levels for active workers. If EPA used respiration rates appropriate for active workers, this should be more clearly communicated.

**B. EPA has overrelied on personal protective equipment and the adequacy of OSHA requirements.**

EPA's risk determinations heavily rely on assumptions that workers, at many or most points in the value chain and lifecycle of TCE, will use personal protective equipment (PPE) (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. (p. 377)

Section 5.A. of these comments provides an analysis EDF conducted of the extent and impact of this over-reliance on PPE.

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<sup>10</sup> National Academies of Sciences, Engineering, and Medicine. 2019. *Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

EPA makes clear that its risk determinations “incorporate consideration of expected PPE (frequently estimated to be a respirator of APF 25 or 50 and gloves with PF 5 – 20)” (p. 35).<sup>11</sup> While EPA does still find unreasonable risk for a significant majority of conditions of use (COUs) – due to the extremely high toxicity of TCE – through its PPE assumptions the agency has dramatically underestimated the risk, which likely will have implications for the risk management stage (see sections 5.A. and 9.A.i. for further discussion).

EPA’s assumptions about PPE use are wholly unsupported and unwarranted. EPA has provided no data or analysis whatsoever to support these sweeping assumptions. In previous draft risk evaluations, the agency has made it clear that it does not have any actual data on respirator or glove use, including data on types used, frequency of use, or prevalence of respiratory protection programs. For TCE, EPA has made some similar statements, but buried them in the Supplemental File: Environmental Releases and Occupational Exposure:<sup>12</sup>

The complexity and burden of wearing respirators increases with increasing APF. The APFs are not to be assumed to be interchangeable for any conditions of use, any workplace, or any worker or ONU. The use of a respirator not necessarily would resolve inhalation exposures since it cannot be assumed that employers have or will implement comprehensive respiratory protection programs for their employees. (p. 32, supplemental file)

Data about the frequency of effective glove use – that is, the proper use of effective gloves – is very limited in industrial settings. Initial literature review suggests that there is unlikely to be sufficient data to justify a specific probability distribution for effective glove use for a chemical or industry. (p. 223, supplemental file)

Instead, EPA simply assumed without evidence that respirators or glove use would result in various levels of protection based on different, purely hypothetical PPE scenarios. EPA then found unreasonable risk only where either: a) the most stringent PPE it could assume was insufficient to mitigate the risk, or b) EPA could not possibly justify any assumption that PPE would be used:

For workers (which are one example of PESS), an unreasonable risk may be indicated when risks are not adequately addressed through expected use of

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<sup>11</sup> Note that we found only a single instance where EPA relied on a protection factor (PF) of 5 for workers (for toner aid; p. 367); otherwise EPA always assumed a PF of 10 or 20.

<sup>12</sup> Supplemental File: Environmental Releases and Occupational Exposure. Available at: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0500-0020>.

workplace practices and exposure controls, including engineering controls or use of personal protective equipment (PPE). (p. 374)

There is considerable evidence of major real world limitations of PPE, with regards to both the extent of use and effectiveness. In fact, OSHA has highlighted the major limitations of reliance on PPE, as has EPA in the recent past. For example, in 2016 OSHA informed EPA that respirators are the “least satisfactory approach to exposure control,” providing the following explanation:

...to be effective, respirators must be individually selected, fitted and periodically refitted, conscientiously and properly worn, regularly maintained, and replaced as necessary. The absence of any one of these conditions can reduce or eliminate the protection the respirator provides.

Respirator effectiveness ultimately relies on the practices of individual workers who must wear them. ... Furthermore, respirators can impose substantial physiological burdens on workers, including the burden imposed by the weight of the respirator; increased breathing resistance during operation; limitations on auditory, visual, and olfactory sensations; and isolation from the workplace environment.<sup>13</sup>

It is also important to recognize that reliance on PPE as a primary measure to protect workers is counter to OSHA’s Industrial Hygiene Hierarchy of Controls (HOC), a long-standing principle that prioritizes measures to eliminate or reduce the presence of a hazard in occupational settings (e.g., substitution/use of less toxic chemicals and institution of engineering controls) over measures that shift burdens onto the workers themselves, such as through reliance on PPE and warning labels. The HOC exemplifies the best available science for creating safe, healthful workplace environments.

EDF previously commented on the serious limitations of labeling and PPE, as well as the importance of adherence to the hierarchy of controls to limit workplace exposures.<sup>14</sup> EDF incorporates and reiterates the points made in those comments here.

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<sup>13</sup> Comment Letter from David Michaels, PhD, MPH, Assistant Secretary, U.S. Dep’t of Labor, Occupational Safety & Health Admin., to James J. Jones, Assistant Administrator, U.S. EPA, Office of Chem. Safety & Pollution Prevention (Oct. 25, 2016), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2014-0650-0041>.

<sup>14</sup> 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

It would be wholly inappropriate for EPA to assume that there is compliance with OSHA's Permissible Exposure Limit (PEL) and that such compliance would be at all health-protective. The PEL, set at 100 ppm, was adopted by OSHA nearly 50 years ago in 1971, and, as EPA acknowledges (p. 468), OSHA itself "has recognized that many of its permissible exposure limits (PELs) are outdated and inadequate for ensuring protection of worker health" and recommends the use of the 2 ppm NIOSH Recommended Exposure Limit (REL). As a further indication of the inadequacy of OSHA's PEL, in the course of developing proposed rules that would have banned particularly high-risk uses of TCE (proposals that have since been abandoned), EPA developed a recommendation for an Existing Chemical Concentration Limit, or "ECEL"<sup>15</sup> of 1 ppb (8-hour time weighted average) as a more current benchmark for workplace exposures.

Despite the severe problems with the OSHA PEL, EPA still seems to assume compliance even with this overly lax standard and ignore real-world workplace monitoring data points it has obtained that are above 100 ppm. EPA did so in its "PEL-capped" analysis, where the agency excluded data samples that were above the PEL (see section 5.D. below). Ironically, notwithstanding its assumption to the contrary (p. 377), EPA's analysis demonstrates that non-compliance has in fact occurred: real-world exposure monitoring data include samples at levels that exceed the PEL.

EPA also mischaracterizes OSHA regulations, which do not in fact require that persons comply with SDSs (and provide broad discretion to employers themselves to decide whether any PPE is needed). In our comments on the 1-Bromopropane Draft Risk Evaluation,<sup>16</sup> EDF commented extensively on why is it inappropriate to assume that workers will be aware of, understand and follow SDS recommendations. In short, not only do OSHA regulations *not* require that persons comply with SDSs, but even if compliance with SDSs were mandatory, reliance on them would still be insufficient to ensure protection given that SDSs are often inaccurate, incomplete, and too technical for many workers to understand. We incorporate our previous comments herein by reference. We also incorporate by reference the comments submitted to EPA by Jonathan Kalmuss-Katz and Randy Rabinowitz on the 1,4-Dioxane Draft Risk Evaluation.<sup>17</sup>

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Amendments to Reporting Requirements for Premanufacture Notices (Nov. 21, 2016), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2014-0650-0052>.

<sup>15</sup> U.S. EPA, Recommendation for an Existing Chemical Exposure Concentration Limit (ECEL) for Occupational Use of Trichloroethylene (TCE) and Sampling and Analysis Methods for TCE (Sept. 2016), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0163-0039>.

<sup>16</sup> Environmental Defense Fund Comments on the Draft Risk Evaluation of 1-Bromopropane, (Oct. 11, 2019), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0047>.

<sup>17</sup> Comments submitted by Jonathan Kalmuss-Katz, Staff Attorney, Earthjustice and Randy Rabinowitz, Executive Director, Occupational Safety & Health (OSH) Law Project, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0021>.

Furthermore, OSHA’s database of inspections demonstrates significant noncompliance with OSHA respiratory protection requirements such as those that apply to TCE. In fiscal year 2018 alone, OSHA cited 2,892 violations of the respiratory protection standard identified in 1,281 separate inspections.<sup>18</sup> Violations of the respiratory standard were the 4<sup>th</sup> most common type of violation in OSHA inspections that year, exceeded only by those for two categories of physical hazard and the Hazard Communication Standard.<sup>19</sup>

Even when respirators and gloves *are* used, workers may still be exposed to TCE. Organic solvents like TCE may breakthrough the carbon or other medium in organic vapor cartridge respirators, and this can occur without providing any indication to the user that the respirator is no longer functioning.<sup>20</sup>

Gloves may also experience chemical breakthrough and provide limited protection from TCE exposure (see p. 221 of Supplemental File: Environmental Releases and Occupational Exposure Assessment). Protection also varies greatly with different glove materials, which EPA alludes to by acknowledging specific glove material types recommended by SDSs (116). Yet, the agency cites no data on actual use of such gloves versus less effective or ineffective alternatives, and instead simply assumes default glove protection factors (PFs) and disregards the potential for occlusion to increase exposure (see section 5.B.iv. for further discussion of EPA’s apparent failure to make risk determinations based on heightened exposure due to occlusion).

In a few places in the draft, EPA very briefly acknowledges some of the limitations of PPE and acknowledges the preferability of other options higher up in the industrial hygiene hierarchy of controls (e.g., p. 119-120). But when it comes to determining risk, those limitations and preferences fall away and EPA exclusively relies on “expected” use of PPE to understate the extent and magnitude of the risks it has identified (see section 5.A. of these comments for an analysis documenting the extent of EPA’s reliance).

EPA’s reliance on PPE is not merely a policy determination. It is a huge assumption that dramatically alters the magnitude of risk presented in EPA’s risk characterizations for TCE. EPA’s reliance on PPE is also a key driver of a large fraction of EPA’s risk determinations for

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<sup>18</sup> U.S. Department of Labor, Occupational Safety and Health Administration, Industry Profile for OSHA Standard 19100134, [https://www.osha.gov/pls/imis/industryprofile.stand?p\\_esize=&p\\_stand=19100134&p\\_state=FE Federal&p\\_type=5](https://www.osha.gov/pls/imis/industryprofile.stand?p_esize=&p_stand=19100134&p_state=FE Federal&p_type=5) (last visited Sept. 9, 2019). These FY 2018 statistics have been replaced with the FY 2019 data and appear not to be currently accessible anymore.

<sup>19</sup> U.S. Department of Labor, Occupational Safety and Health Administration, Top 1- Most Frequently Cited Standards, <https://www.osha.gov/top10citedstandards> (last visited Nov. 26, 2019).

<sup>20</sup> United States Air Force AFIOH, 2004. “Estimating Organic Vapor Cartridge Service Life,” p. 29. Available at: <https://apps.dtic.mil/dtic/tr/fulltext/u2/a439710.pdf>.

workers even though EPA has no actual data on the extent or effectiveness of PPE use. EPA's reliance on PPE leads the agency to understate the extent and magnitude of the risk where it does identify unreasonable risk. *See* section 5.A. of these comments. EPA's failure to provide *any* supporting data that PPE is universally used and effective, as assumed in its risk determinations for many conditions of use (COUs), is a glaring flaw in this draft risk evaluation.

Section 5.A. of these comments presents an analysis showing that, for many of the endpoints and exposure routes under the conditions of use of TCE, EPA found that they present no unreasonable risk only by assuming that workers wear effective PPE to protect against inhalation or dermal exposures. For most of those conditions of use where EPA did identify unreasonable risk, it was compelled to do so because even the most stringent level of respiratory or dermal PPE EPA examined and assumed would be used was insufficient to eliminate that risk.

### **C. The SACC must address the scientific consequences of EPA's "policy" determinations.**

EPA has publicly stated that a number of the topics discussed at past SACC meetings on 1,4-dioxane and 1-bromopropane (1-BP) are in the realm of policy and are therefore not relevant to the SACC's charge. These include:

- EPA's decision to exclude all general population risks arising from exposures from releases to land, air, and water based on the assumption that other statutes adequately address the exposures;
- EPA's decision to assume that PPE is always used and effective under many conditions of use; and
- EPA's decision to use a benchmark cancer risk level of  $1 \times 10^{-4}$  to define unreasonable risk to workers.

EDF strongly disagrees that these issues are beyond the scope of the SACC. In fact, they fall squarely within the SACC's charge. All three decisions have major direct scientific consequences, as they clearly lead to underestimations of chemicals' risk – to the environment, the general population, workers, and vulnerable subpopulations. In the Final SACC Reports for 1,4-dioxane, 1-BP, and methylene chloride,<sup>21</sup> the SACC appropriately addressed some of these

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<sup>21</sup> *See* SACC Final Report/Meeting Minutes for 1,4-Dioxane, transmitted Oct. 31, 2019, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064>; Meeting Minutes and Final Report for the SACC on 1-Bromopropane, transmitted Dec. 12, 2019, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061>; Meeting Minutes and Final Report for the SACC on Methylene Chloride, transmitted March 2, 2020, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0080>.

issues and should continue doing so in future reports with a particular emphasis on how those determinations affect the scientific accuracy and legitimacy of the risk evaluations.

All three of EPA's decisions described above represent assumptions that EPA has not verified or adequately explained, and that introduce major uncertainty into its risk evaluation that EPA has not analyzed. It is vital that the SACC consider and address in its report the scientific consequences of these assumptions and decisions on EPA's characterization of exposure, hazard, and risk. Each of these assumptions are addressed below.

*First*, the statutory-based exclusions. As described in section 2.B. of these comments, EPA has asserted that exposures to the general population are "adequately managed" without any analysis whatsoever of the standards under the other statutes, including standards that are not strictly health based, unlike TSCA's standard. EPA devoted less than four pages to justify its decision to eliminate entire pathways, and provided no data or analysis of the exposures and risks that remain and their contribution to total exposure and risk.<sup>22</sup>

EPA has failed to provide any scientific rationale for this assumption, and the SACC has been charged with commenting precisely on the adequacy of the support EPA has provided for just such assumptions.

*Second*, as discussed in further detail in section 1.B. of these comments, EPA frequently assumes PPE is used and effective in order to find no unreasonable risk to workers, even though EPA has stated elsewhere (albeit buried in the Supplemental File: Environmental Releases and Occupational Exposure) that it does not have data on the extent of use and effectiveness of gloves or existence of comprehensive respiratory protection programs.

In order for the SACC to fully evaluate this assumption, the SACC should request that EPA provide any feedback EPA has received from OSHA and NIOSH on its assumption regarding PPE use, and more generally, any input they have provided EPA regarding the extent and sufficiency of OSHA's authorities.

*Third*, EPA's unprecedented use of 1 in 10,000 as the cancer risk benchmark for workers also clearly underestimates risk, and flies in the face of EPA's longstanding policy "that it should reduce risks to less than  $1 \times 10^{-6}$  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). Workers are specifically identified under TSCA as a vulnerable subpopulation warranting special protection. See section 7.A.ii. for more detail on this issue.

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<sup>22</sup> Those four pages were in the problem formulation for methylene chloride, and the draft risk evaluation merely alluded to that explanation with no additional analysis. See Methylene Chloride Problem Formulation at pp. 54-57 and the draft risk evaluation at p. 33.

In sum: TSCA specifically states that the purpose of the SACC is to provide advice on “scientific and technical aspects” related to implementation of TSCA, and EPA’s sweeping assumptions regarding exposures from environmental releases, PPE use, and adequacy of reliance on a less protective cancer risk benchmark for workers have direct impacts on the scientific integrity of EPA’s implementation of TSCA.

The SACC needs to address the scientific consequences of each of these decisions. At the very least, it is the SACC’s responsibility to state clearly in its report that these assumptions result in serious underestimations of risk.

## **2. EPA has inappropriately or illegally excluded conditions of use and exposures.**

### **A. EPA failed to analyze certain reasonably foreseen conditions of use.**

In the problem formulation, EPA excluded “paints and coatings for consumer use” on the basis that TCE is no longer used in the circumstances. Problem Formulation at p.20. EPA notably continues to analyze these conditions of use in the industrial and commercial context. *See* draft risk evaluation at p.50. EPA should analyze the consumer uses in these circumstances because TCE’s use in the industrial and commercial context makes its at least reasonably foreseen that TCE is or could be used in the same manner in the consumer context.

While compelling evidence of the absence of consumer products could establish that these circumstances are not “known” conditions of use, EPA has not addressed whether these circumstances are “reasonably foreseen” conditions of use. *See* 15 U.S.C. § 2602(4) (“The term ‘conditions of use’ means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or *reasonably foreseen* to be manufactured, processed, distributed in commerce, used, or disposed of.”) (emphasis added). TCE is used for these specific purposes in the industrial and commercial context, and therefore it is at least reasonably foreseen that it is or could be used in the same manner in consumer products.

Congress included “reasonably foreseen” circumstances within TSCA with the express goal of ensuring that EPA swept more broadly than known (or intended) uses; EPA cannot evade that duty by limiting its analysis to conditions of use with evidence of current, ongoing use—such an interpretation would effectively limit EPA’s analysis to “known” uses. While there may well be circumstances in which a use that is not currently occurring could be said to be not “reasonably foreseen” at this time, the term surely cannot be read in such a way that only uses that are known to be current are “reasonably foreseen” as that would read it out of existence and collapse the inquiry to one where a use must be “known” to be considered “reasonably foreseen.”

Reasonably foreseen is a term of art with a long history in the law; it is well established under the law that “[a] natural and probable consequence is a foreseeable consequence. But to be

reasonably foreseeable [t]he consequence need not have been a strong probability; a possible consequence which might reasonably have been contemplated is enough.” *People v. Medina*, 209 P.3d 105, 110 (Cal. 2009) (internal citations and quotation marks omitted). When a chemical is used in a commercial setting and where “there is no evidence to show that the manufacturer, wholesaler, or retailer of a hazardous substance sought to limit sales of the product to industrial or professional users, it is reasonably foreseeable that household consumers will have access to the product.” *Canty v. Ever-Last Supply Co.*, 296 N.J. Super. 68, 78-79 (N.J. Super. Ct. 1996). Even where a product is “labeled for industrial use,” it may be reasonably foreseeable that the product may ultimately be used by a consumer. *See No. 98-1979 v. Sunnyside Corp.*, 2000 Wisc. App. LEXIS 118, \*12 (Ct. of Appeals WI, Feb. 15, 2000). Here, given TCE’s industrial and commercial uses, the potential for these uses to be expanded to consumer use is reasonably foreseeable.

#### **B. EPA has inappropriately excluded exposures based on other statutes.**

Referencing its earlier problem formulation, EPA has excluded from its risk evaluation all general population exposures to TCE, based on EPA’s assertion – unsupported by any actual data or analysis – that the exposure pathways for the general population are “adequately assess[ed] and effectively manage[d]” under other environmental statutes (p. 35). Specifically, EPA states:

Exposure pathways to the general population are covered by other statutes and consist of: the ambient air pathway (i.e., TCE is listed as a HAP in the Clean Air Act (CAA)), the drinking water pathway (i.e., National Primary Drinking Water Regulations (NPDWRs) are promulgated for TCE under the Safe Drinking Water Act), ambient water pathways (i.e., TCE is a priority pollutant with recommended water quality criteria for protection of human health under the CWA), the biosolids pathway (i.e., the biosolids pathway for TCE is currently being addressed in the CWA regulatory analytical process), disposal pathways (TCE disposal is managed and prevented from further environmental release by RCRA and SDWA regulations). As described above, other environmental statutes administered by EPA adequately assess and effectively manage these exposures. Therefore, EPA did not evaluate hazards or exposures to the general population in this risk evaluation, and there is no risk determination for the general population (p. 379; see also 35, 276).

EPA therefore excluded from the draft risk evaluation all general population exposure through air, water, and land to TCE.

Aside from the absent legal basis, these exclusions present significant health concerns. For example, in the problem formulation for TCE (p. 54), EPA explicitly relies on the Clean Air Act

(CAA) to dismiss the need to assess exposures to TCE from air emissions. TCE is regulated as a hazardous air pollutant (HAP) under the CAA, but the standards under the CAA for HAPs are set for individual source categories, meaning that the exposures to TCE from all sources in combination are never considered. In a recent proposed rule under the CAA for a source category for another chemical, EPA has stated that:

Although we are interested in placing source category and facility-wide HAP risk in the context of total HAP risk from all sources combined in the vicinity of each source, we are concerned about the uncertainties of doing so. Estimates of total HAP risk from emission sources other than those that we have studied in depth during this RTR review would have significantly greater associated uncertainties than the source category or facility-wide estimates. Such aggregate or cumulative assessments would compound those uncertainties, making the assessments too unreliable.

National Emission Standards for Hazardous Air Pollutants: Rubber Tire Manufacturing Residual Risk and Technology Review, 84 Fed. Reg. 58,268, 58,273 (proposed Oct. 30, 2019). This explanation of EPA's approach to assessments under the CAA makes clear that EPA does not look at overall risk from a chemical substance. Therefore, EPA's approach to this and its other draft risk evaluations under TSCA ensures that EPA *never* evaluates, and the public never finds out, the risk from all air emissions of TCE or any other chemical substance. The SACC has previously noted the flaws in this approach to EPA.<sup>23</sup>

In addition, even by its own account, EPA's CAA regulations do not eliminate risk to exposed populations. For example, when EPA promulgated a regulation "to limit emissions of methylene chloride (MC), trichloroethylene (TCE) and perchloroethylene (PCE) from facilities engaged in halogenated solvent cleaning," EPA did not eliminate cancer risks. National Air Emission Standards for Hazardous Air Pollutants: Halogenated Solvent Cleaning, 72 Fed. Reg. 25,138 (May 3, 2007). Instead, EPA adopted standards that it acknowledged would leave the maximum individual risk of cancer at "between 20 and 50-in-a-million and the total number of people with risks greater than 1-in-a-million would \*\*\* be \*\*\* between 500,000 and 1,000,000." *Id.* at 25,148. Thus, by EPA's own account, its CAA regulation of TCE did not eliminate all risk from just these facilities, much less consider how exposure to TCE from the regulated facilities might combine with exposures from other facilities and sources to increase overall risk.

EPA has also failed to acknowledge that the requirements to address human and environmental health risks it relies on derive from statutes that establish criteria different than those under

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<sup>23</sup> SACC July 2019 Meeting Minutes and Final Report Docket p. 18 (Oct. 31, 2019), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063>.

TSCA.<sup>24</sup> 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.

The releases and 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 existing regulations under other laws, facilities release 2 to 3 million pounds annually of TCE to air, water and land. EPA's approach effectively reduces this quantity to zero.

**C. EPA's failure to consider general population exposures to TCE ignores numerous major exposure pathways.**

EPA's decision to exclude any consideration of general population exposure to TCE in the draft risk evaluation ignores the exposures of millions of Americans to one of the most pervasive and toxic chemical pollutants in our environment. This omission also ignores exposures to the most vulnerable subpopulations, the developing fetus, infants, and children. These omissions violate the intent of the Lautenberg Act's 2016 amendments to TSCA and are contrary to the core mission of EPA to protect public health.

EPA and the Centers for Disease Control/Agency for Toxic Substances and Disease Registry (CDC/ATSDR) have documented the following key exposure pathways:<sup>25</sup>

*Outdoor Air:* EPA, CDC/ATSDR and most states have documented TCE concentrations in ambient air, with elevated levels around sources and in highly populated areas.

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<sup>24</sup> EDF has addressed these limitations in greater detail in prior comments. *See, e.g.*, EDF Comment on the 1,4-dioxane Draft Risk Evaluation pp. 113-31, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0058>.

<sup>25</sup> The information presented in this subsection is drawn from EPA's (2011) Toxicological Review of Trichloroethylene, available at <https://www.epa.gov/iris/supporting-documents-trichloroethylene>.

*Indoor Air and Vapor Intrusion:* TCE is pervasive in indoor air at concentrations documented to be several times higher than outdoor levels due to consumer products, vapor intrusion from subsurface contamination, and volatilization from contaminated drinking water.

*Groundwater and Drinking Water Wells:* CDC/ATSR has reported that TCE is the most frequently detected chemical contaminant in groundwater. Shallow private wells used for drinking water and irrigation are particularly vulnerable. These wells are not monitored nor covered by the Safe Drinking Water Act.

*Food:* TCE has been found in a wide variety of foods. The FDA Total Diet Program has measured TCE throughout the food supply including butter, cheese, fruits, and cereal and grain products.

*Breast Milk and Formula:* TCE has been detected in breast milk in the general population. Formula fed infants are also vulnerable because of the pervasive contamination of drinking water and their high ingestion rate.

**D. EPA needs to analyze those potentially exposed or susceptible subpopulations that face greater exposure due to their proximity to conditions of use.**

TSCA § 3(12) states that “the term ‘potentially exposed or susceptible subpopulation’ means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health 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). In its draft risk evaluation, EPA erroneously limits its analysis to only half of this definition; EPA discusses whether persons might face greater susceptibility to TCE, but, outside of its consideration of worker and consumer exposures, EPA does not consider whether subpopulations may face a greater risk due to greater exposure. EPA must consider and analyze each of these types of subpopulations.

EPA must identify those who face greater exposures due to their proximity to conditions of use as a “potentially exposed or susceptible subpopulation” since they are a “group of individuals within the general population identified by the Administrator who, due to \*\*\* greater exposure, *may* be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture.” 15 U.S.C. § 2602(12) (emphasis added). Notably, in the problem formulations, EPA seemed to acknowledge that it should analyze these vulnerable subpopulations. *See, e.g.*, Problem Formulation for TCE at pp. 38-39 (“Other groups of individuals within the general population who may experience greater exposures due to their proximity to conditions of use that result in releases to the environment and subsequent

exposures (e.g., individuals who live or work near manufacturing, processing, use or disposal sites).”).

In the draft risk evaluation, EPA in a few places makes passing reference to such exposures. For example, it notes that “[e]xposures of TCE would be expected to be higher amongst groups living near industrial facilities” (p. 186). And EPA acknowledges that it has underestimated consumer exposure due to its approach:

Background levels of TCE in indoor and outdoor air are not considered or aggregated in this assessment; therefore, there is a potential for underestimating consumer inhalation exposures, particularly for populations living near a facility emitting TCE... . (p. 177)

But EPA does not identify these subpopulations as potentially exposed or susceptible subpopulations, or provide any analysis of the extent to which these or other subpopulations living in proximity to the conditions of use are at greater risk due to greater exposure.

EPA has failed to provide any factual justification for excluding such exposures. EPA should analyze these exposures and should analyze the associated risks to these *potentially* exposed subpopulations. EPA’s failure to consider this relevant aspect of the problem is arbitrary and capricious.

In order to accurately assess the exposure of these subpopulations, EPA should analyze the environmental pathways that lead to their exposure. Thus, EPA should not exclude those pathways for the reasons given above, and in addition, EPA cannot rationally evaluate the greater exposure these subpopulations face without analyzing these pathways. Ignoring these subpopulations violates EPA’s duty to consider potentially exposed or susceptible subpopulations.

As part of this analysis, EPA should identify people living near all disposal sites as potentially exposed or susceptible subpopulations. These groups include (but are not limited to) those living near Superfund sites.<sup>26</sup> To be clear, many disposal sites are associated with activities that reflect ongoing or prospective manufacturing, processing, distribution, or use, so EPA must also analyze those disposals and disposal sites and subpopulations living in proximity to them.

**E. EPA has failed to consider exposure to background levels of TCE.**

EPA states (p. 177):

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<sup>26</sup> See Appendix 2 for a list of the 731 active Superfund sites containing TCE.

Background levels of TCE in indoor and outdoor air are not considered or aggregated in this assessment; therefore, there is a potential for underestimating consumer inhalation exposures, particularly for populations living near a facility emitting TCE or living in a home with other sources of TCE, such as TCE-containing products stored in the home.

EPA must justify this decision, given that subpopulations living in proximity to such exposure sources represent potentially exposed or susceptible subpopulations that must be considered under TSCA (see section 2.D. of these comments).

Should the Agency nevertheless decide to proceed with this exclusion, at a minimum EPA must quantify the number of people expected to experience substantial exposures to background concentrations of TCE in indoor and outdoor air to allow the public to understand the magnitude of the exposures being omitted as a result of the Agency's decision. Furthermore, EPA should conduct sensitivity analyses to quantify the potential extent of underestimation due to excluding these background exposures.

#### **F. EPA excluded a number of workplace-related exposure scenarios.**

EPA excluded a number of reasonably foreseen conditions of use in the workplace that should have been evaluated. During the SACC meeting to peer-review the 1,4-dioxane draft risk evaluation, concerns were raised about a number of exposure scenarios that the agency failed to consider, each of which equally applies to TCE. Among those discussed are:

- Exposures from spills in the workplace, especially considering the potential for inhalation exposure from evaporation for maintenance workers cleaning up spills and leaks;<sup>27</sup>
- “Take-home exposures,” whereby the family of a worker, including children, may be exposed via contact with the worker's contaminated clothing or skin; and
- Exposures of workers at small or medium facilities where assumptions of routine PPE use or other protections are even less likely to be valid.

With regards to the last point, as documented in section 5.A. of these comments, while we recognize that EPA did not assume use of respirators by workers under five conditions of use (COUs) presenting occupational exposure potential, EPA still assumed universal use and effectiveness of respirators in all of the other such COUs. SACC members peer-reviewing 1,4-

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<sup>27</sup> While the Conceptual Model on page 57 indicates that fugitive emissions were considered (which the agency defines as “those that are not stack emissions, and include fugitive equipment leaks from valves, pump seals, flanges, compressors, sampling connections and open-ended lines; evaporative losses from surface impoundment and *spills*; and releases from building ventilation systems,” emphasis added), it is unclear whether or how EPA actually addressed spills in the draft risk evaluation.

dioxane expressed concern that even if one assumes that PPE is typically used in larger, industrial facilities, smaller facilities are much less likely to require routine and effective use of protective equipment or to employ engineering controls, like closed systems. Workers at any facility – whether small, medium, or large – where use of effective PPE cannot be thoroughly documented should be considered vulnerable subpopulations and the risk they face be specifically assessed. For these subpopulations, EPA must determine risk based on exposures without assuming any use of PPE.

“Conditions of use” are broadly defined under TSCA to mean “the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or *reasonably foreseen* to be manufactured, processed, distributed in commerce, used, or disposed of.” 15 U.S.C. § 2602(4) (emphasis added). Each of the circumstances described above—spills, take home exposures, and exposures without appropriate PPE—is a “reasonably foreseen” aspect of the circumstances under which methylene chloride is manufactured, processed, distributed, used, or disposed of.<sup>28</sup> It is well established under the law that “[a] natural and probable consequence is a foreseeable consequence. But to be reasonably foreseeable [t]he consequence need not have been a strong probability; a possible consequence which might reasonably have been contemplated is enough.” *People v. Medina*, 46 Cal. 4th 913, 920 (Cal. 2009) (internal citations and quotation marks omitted).

“Reasonably foreseen” is a term of art with a long history in the law, and EPA should turn to the ample precedent interpreting this language to inform implementation of this legal requirement. Spills and leaks are undoubtedly reasonably foreseeable, and indeed, when preparing environmental impact statements (EISs) for federal projects, the federal government regularly analyzes the potential for spills and leaks because they are reasonably foreseen aspects of such projects. *See, e.g., Sierra Club v. Clinton*, 689 F. Supp. 2d 1123, 1139 (D. Minn. 2010) (describing analysis of potential for leaks and spills).

And in the tort context, courts have found that spills and leaks can be reasonably foreseen. *See, e.g., Monroe v. Safeway, Inc.*, 2004 Wash. App. LEXIS 672, \*6 (Ct. Appeals Wash. 2004); *Ceasar v. Wal-Mart Stores, Inc.*, 787 So. 2d 582, 588 (Ct. Appeals. La. 2001) (finding spill reasonably foreseeable); *Lumbermens Mut. Cas. Co. v. Banco Espanol De Credito*, 2006 U.S. Dist. LEXIS 75728, \*25 (S.D.N.Y. Oct. 13, 2006) (describing leak as reasonably foreseeable);

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<sup>28</sup> During the Science Advisory Committee on Chemicals (SACC) meeting on methylene chloride, EPA’s Dr. Barone stated that “spills are not a condition of use.” We disagree; spills constitute a “reasonably foreseen \*\*\* circumstance under which a chemical is manufactured, processed, distributed, used, or disposed of.” and lead to exposures that need to be considered in a risk evaluation.

*Goehler v. Wal-Mart Stores, Inc.*, 2000 U.S. App. LEXIS 20932, \*1-2 (4th Cir. Aug. 17, 2000) (same).

Take-home exposure and exposure of persons not using PPE are equally reasonably foreseen.

**3. EPA is justified in adopting a linear, no-threshold approach for TCE's carcinogenicity.**

**A. There is strong support for TCE's cancer classification and a mutagenic mode of action for kidney cancer.**

In the draft risk evaluation, EPA correctly concludes that TCE is linked to non-Hodgkin's lymphoma, kidney, and liver cancer (see section 3.2.3.2, pp. 218-219 and section 3.2.4.2, pp. 225-226).

EPA's decision to affirm TCE's carcinogenicity and carry forward cancer hazard for dose-response modeling is wholly consistent with numerous other classifications:

- The International Agency for Research on Cancer (IARC) has stated that TCE is "*carcinogenic to humans (Group 1)*," based on sufficient evidence in both humans and experimental animals.<sup>29</sup>
- The National Toxicology Program's (NTP) *Report on Carcinogens* concluded that TCE is "*known to be a human carcinogen* based on sufficient evidence of carcinogenicity from humans."<sup>30</sup>
- EPA's IRIS program has classified TCE as "*carcinogenic to humans by all routes of exposure*."<sup>31</sup>

The Agency's conclusion in the draft risk evaluation is also aligned with the EPA's 2014 Work Plan Chemical Risk Assessment of TCE as well as the recent 2019 ATSDR toxicological profile of TCE.<sup>32</sup>

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<sup>29</sup> IARC Working Group on the Evaluation of Carcinogenic Risks to Humans.

"Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents." *IARC monographs on the evaluation of carcinogenic risks to humans* 106 (2014).

<sup>30</sup> Nat'l Toxicology Program, *Report on Carcinogens Monograph for Trichloroethylene*, [https://ntp.niehs.nih.gov/ntp/roc/monographs/finaltce\\_508.pdf](https://ntp.niehs.nih.gov/ntp/roc/monographs/finaltce_508.pdf)

<sup>31</sup> EPA IRIS website,

[https://cfpub.epa.gov/ncea/iris/iris\\_documents/documents/toxreviews/0199tr/0199tr.pdf](https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf).

<sup>32</sup> Agency for Toxic Substances and Disease Registry (ATSDR). 2019. Toxicological profile for Trichloroethylene (TCE). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Moreover, EPA appropriately concludes that TCE is genotoxic, stating “there is sufficient evidence that TCE-induced kidney cancer operates primarily through a mutagenic mode of action” (p. 30). EPA also states (p. 227):

The predominant mode of action (MOA) for kidney carcinogenicity involves a genotoxic mechanism through formation of reactive GSH metabolites (e.g., DCVC, DCVG). This MOA is well-supported, as toxicokinetic data indicates that these metabolites are present in both human blood and urine, and these metabolites have been shown to be genotoxic both in vitro and in animal studies demonstrating kidney specific genotoxicity (U.S. EPA, 2011e).

Importantly, the Agency also states (p. 256) that while there is some evidence for the involvement of cytotoxicity and regenerative proliferation, these processes do not have:

the extent of support as for a mutagenic mode of action. In particular, data linking TCE-induced proliferation to increased mutation or clonal expansion are lacking, as are data informing the quantitative contribution of cytotoxicity. Because any possible involvement of a cytotoxicity mode of action would be additional to mutagenicity, the dose-response relationship would nonetheless be expected to be linear at low doses. Therefore, the additional involvement of a cytotoxicity mode of action does not provide evidence against the use of linear extrapolation from the POD.

This conclusion regarding a lack of evidence for alternative MOAs is also consistent with other findings of authoritative agencies. For example, IARC determined that “[t]he data supporting the non-genotoxic mechanisms of kidney carcinogenesis were limited.”<sup>33</sup>

Overall, given the strong evidence for TCE’s carcinogenicity and mutagenicity, we strongly support the agency’s decision to adhere to the *EPA Guidelines for Carcinogen Risk Assessment* and use the approach of linear non-threshold extrapolation in the cancer risk modeling for TCE.

**B. The scientifically sound and health-protective approach is to use linear extrapolation in cancer dose-response modeling for TCE.**

*i. Justification based on existing guidance*

The information presented above: 1) demonstrates that evidence supports a genotoxic MOA for TCE, and 2) casts doubt on the plausibility of alternative MOAs. Even were the evidence

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<sup>33</sup> IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. "Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents." *IARC monographs on the evaluation of carcinogenic risks to humans* 106 (2014).

deemed insufficient to identify with certainty a genotoxic MOA, there is longstanding EPA policy guidance and precedent supporting a default to a no-threshold, linear extrapolation method for cancer dose-response modeling.

The agency's own 2005 cancer guidelines state that:

When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach.<sup>34</sup>

EPA must follow its guidance documents in preparing the final risk evaluation. “An agency may not ... depart from a prior policy *sub silentio* or simply disregard rules that are still on the books.” *FCC v. Fox TV Stations, Inc.*, 556 U.S. 502, 515 (2009). EPA's guidance documents reflect the considered judgment of the agency on major factual issues, and an agency may not lightly adopt new policies reflecting contradictory factual findings without providing a detailed justification for the shift in position. *Id.* Moreover, EPA's Risk Evaluation Rule provides that “EPA guidance will be used, as applicable where it represents the best available science appropriate for the particular risk evaluation.” 40 C.F.R. § 702.41(a)(2). Thus, EPA must use its guidance in this risk evaluation unless EPA can establish that the guidance does not represent the best available science appropriate for this particular risk evaluation.

*ii. Justification based on human population variability and other real-world considerations to protect public health*

EPA must employ health-protective approaches to dose-response modeling, as described at length in the National Research Council's report, *Science and Decisions: Advancing Risk Assessment*. In this report, the NRC committee specifically provides important perspective on the need to conduct a linear extrapolation at the population level, even where a threshold might theoretically exist. The authors state, for example, that:<sup>35</sup>

- “Human variability with respect to the individual thresholds for a nongenotoxic cancer mechanism can result in linear dose-response relationships in the population.”
- “In the laboratory, nonlinear dose-response processes ... may be found to cause cancer in test animals. However, given the high prevalence of these background processes, given

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<sup>34</sup> U.S. EPA, *Guidelines for Carcinogen Risk Assessment* at pp. 3-21 (Mar. 2015), [https://www.epa.gov/sites/production/files/2013-09/documents/cancer\\_guidelines\\_final\\_3-25-05.pdf](https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf).

<sup>35</sup> NAT'L RESEARCH COUNCIL, *SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT* at chp. 5, pp. 130-131 (2009), <https://www.ncbi.nlm.nih.gov/pubmed/25009905>.

cancer as an end point, and given the multitude of chemical exposures and high variability in human susceptibility, the results may still be manifested as low-dose linear dose-response relationships in the human population.”

Overall, the NRC report concluded that “\*\*\*cancer and noncancer responses [to chemical exposures] be assumed to be linear as a default\*\*\*.”<sup>36</sup> The NRC committee called for a unified approach using linear extrapolation to account for both background exposures and the wide range of variability in individual susceptibility. It argued that this approach also improves the risk characterization and ultimately risk management decisions by providing quantification of excess population risk rather than a margin of exposure.

In their *State-of-the-science workshop report: issues and approaches in low-dose-response extrapolation for environmental health risk assessment*, White et al. (2009)<sup>37</sup> also highlight that (*emphasis added*):

At the human population level \*\*\* biological and statistical attributes tend to smooth and linearize the dose-response relationship, obscuring thresholds that might exist for individuals. Most notable of these attributes are population variability, additivity to preexisting disease or disease processes, and background exposure-induced disease processes.

The 2016 amendments to TSCA made explicit and strengthened EPA’s obligation to consider risks to and protect subpopulations that may be more exposed or more susceptible to the effects of chemical exposure than the general population. To meet this statutory requirement, EPA must use a linear non-threshold modeling approach.

In summary, given 1) existing agency guidance, 2) the many sources of variability in the human population, 3) TSCA’s mandate to protect “potentially exposed or susceptible subpopulations,” and 4) the clear presence of individuals with preexisting health conditions, metabolic or genetic variability, or other factors that make them more susceptible to methylene chloride exposure (see, for example, pp. 275, 386), the use of the linear extrapolation is the only appropriate option for cancer dose-response modeling. EPA also must use this approach to cancer dose-response modeling to comply with EPA’s duty to consider the “best available science” under TSCA § 26(h).

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<sup>36</sup> *Ibid.* at chp. 5, p. 180.

<sup>37</sup> Ronald H. White, et al., *State-of-the-science workshop report: issues and approaches in low-dose-response extrapolation for environmental health risk assessment*, 117:2 ENVTL. HEALTH PERSPECTIVES 283-87 (2008), <https://www.ncbi.nlm.nih.gov/pubmed/19270800>.

**4. EPA’s human health hazard assessment raises significant questions and concerns, while exhibiting positive improvements in a few areas.**

**A. EPA has failed to include any estimate of acute cancer risks.**

Despite EPA’s acknowledgment that the weight of the scientific evidence indicates TCE is a mutagenic carcinogen and that linear extrapolation is warranted (p. 30), the agency has chosen not to estimate cancer risks based on acute exposures. As an explanation, EPA states that the “extrapolation of lifetime theoretical excess cancer risks to single exposures has great uncertainties” and that “the relationship between a single short-term exposure to TCE and the induction of cancer in humans has not been established in the current scientific literature (p. 251).

However, the National Research Council (NRC) states (*emphasis added*):<sup>38</sup>

Guidance on the development of short-term exposure levels, published by the NRC, identified cancer as one of the potential adverse health effects that might be associated with short-term inhalation exposures to certain chemical substances (NRC 1993a). That guidance document discusses and recommends specific risk-assessment methods for known genotoxic carcinogens and for carcinogens whose mechanisms are not well understood. As a first approximation, *the default approach involves linear low-dose extrapolation from an upper confidence limit on theoretical excess risk*. Further, the NRC guidance states that *the determination of short-term exposure levels will require the translation of risks estimated from continuous long-term exposures to risks associated with short-term exposures*. Conceptually, the approach recommended for genotoxic carcinogens adopted the method developed by Crump and Howe (1984) for applying the linearized multistage model to assessing carcinogenic risks based on exposures of short duration.

Later in the same document (p. 118), the NRC summarizes: “Guidance published by the NRC (1993a) states that the setting of AEGLs (CEELs) [acute exposure guideline levels (for what are termed “community emergency exposure levels”)] should involve linear low-dose extrapolation from an upper confidence limit on excess risk for genotoxic carcinogens.”

As stated in this NRC report, the decision to conduct such extrapolation and modeling should be based on the “sound biological and statistical principles.” EDF is concerned that EPA did not sufficiently consider such principles related to mode-of-action in deciding not to model acute

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<sup>38</sup> Nat’l Research Council, *Standard operating procedures for developing acute exposure guideline levels for hazardous chemicals*, pp. 111-112 (2001), <https://www.epa.gov/aegl/standing-operating-procedures-developing-acute-exposure-guideline-levels-aegls-hazardous>.

cancer risk based on chronic exposure data. In particular, given that 1) the agency recognizes that “there is sufficient evidence that TCE-induced kidney cancer operates primarily through a mutagenic mode of action” (p. 233) and 2) a mutagenic MOA suggests a role for “a single direct reaction, specifically, a single hit in a single target (Kirsch-Volders et al., 2000),”<sup>39</sup> a linear low-dose extrapolation from chronic to acute exposures would be the appropriate approach to take for TCE.

It is possible, though, that even a linear extrapolation from chronic cancer bioassays may underestimate the cancer risk of short-term exposures. Halmes et al., 2000 lends support to the potential for short-term exposures to result in similar or higher cancer risks than even chronic lifetime exposures.<sup>40</sup> The study used NTP data where both shorter term and full lifetime studies had been conducted.

EPA’s current approach assumes acute exposures to TCE, including to consumers, pose *zero* cancer risk – an assumption that is clearly not warranted based on the weight of the evidence. EPA needs to apply an extrapolation that provides a scientifically sound estimate for cancer risk from acute and short-term exposures to TCE. As EDF stated in our comments on EPA’s problem formulations (p. 81):

EPA must closely examine any effect it believes to arise only from chronic exposures to determine whether in fact this is true across the diverse human population, including where potentially exposed or susceptible subpopulations may be at increased risk for effects after shorter periods of exposure compared to the general population.

**B. Several critical toxicokinetic issues are raised but not all are sufficiently addressed in the draft risk evaluation.**

The draft risk evaluation includes several toxicokinetic considerations that bear directly on characterizations and estimates of TCE risk, identified and discussed below.

*i. Absorption via the inhalation and dermal routes*

EPA appropriately assumes 100% absorption of TCE via the inhalation and occluded dermal routes. The 2011 IRIS toxicological review of TCE provides extensive scientific support and discussion for these assumptions (see sections 3.1.2 and 3.1.3).

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<sup>39</sup> Zoë Gillespi, et al., *Risk assessment approaches for carcinogenic food contaminants*, 1:1 INT’L FOOD RISK ANALYSIS J. 1-18 (2011), <https://hrcak.srce.hr/file/107066>.

<sup>40</sup> N. Christine Halmes, et al., *Reevaluating cancer risk estimates for short-term exposure scenarios*, 58:1 TOXICOLOGICAL SCIENCES 32-42 (2000), <https://academic.oup.com/toxsci/article/58/1/32/1658920/#24341943>.

*ii. Important metabolic differences across the human population*

EPA acknowledges important pathways—cytochrome P450 (CYP) oxidation pathway and glutathione (GSH) conjugation pathway—that are involved in TCE metabolism and lead to the generation of known toxic metabolites including dichloroacetic acid (DCA) and trichloroacetic acid (TCA). (p. 204-207). The agency further acknowledges variability across the human population with regard to these pathways:

Significant variability may exist in human susceptibility to TCE given the existence of CYP isoforms and the variability in CYP-mediated TCE oxidation. (p. 204)

Compared to the CYP oxidation pathway, there appear to be more significant sex and species differences in TCE metabolism via the GSH pathway. (p. 205)

Significant variability in human susceptibility to TCE toxicity may result from differences in metabolic potential, given the existence of CYP isoforms and the variability in CYP-mediated TCE oxidation. Increased enzymatic activity of cytochrome P450 2E1 (CYP2E1) and glutathione-S-transferase (GST) polymorphisms may influence TCE susceptibility due to effects on the production of toxic metabolites. (p. 234)

EPA's PBPK model attempts to account for these metabolic differences (see for example section 3.2.2.1, pp. 206-209). However, acknowledged data gaps introduce uncertainty regarding the extent to which the PBPK model sufficiently addresses these important variabilities that make individuals differentially susceptible:

In general, an attempt was made to use tissue-specific dose-metrics representing particular pathways or metabolites identified from reasonably available data on the role of metabolism in toxicity for each endpoint....The selection was limited to dose metrics for which uncertainty and variability could be adequately characterized by the PBPK model. For most endpoints, sufficient information on the role of metabolites or mode of action was not available to identify likely relevant dose metrics... (p. 206)

EPA should more fully address the extent to which the PBPK model addresses the acknowledged uncertainty and does so in a manner that is health-protective, including specifically for susceptible populations.

*iii. Incorporation of pregnancy in the PBPK model*

EPA states that “[f]or developmental toxicity endpoints, the TCE PBPK model did not incorporate a pregnancy model to estimate the internal dose of TCE in the developing fetus” (p

207). In the recent NASEM *Review of the Department of Defense's Approach to Deriving an Occupational Exposure Level for Trichloroethylene*, the review committee raised a concern on the same topic:<sup>41</sup>

Specifically, the PBPK model does not have a component designed for pregnant or lactating animals, which is a potential limitation for internal dose metric determinations for pregnant or nursing mothers exposed to TCE in the workplace. PBPK models have been developed for pregnant rats, lactating rats, and nursing pups (e.g., Fisher et al. 1989, 1990). DOD should improve transparency in its choice of the PBPK model by discussing the reasons for, and potential impact of, not accounting for anatomic, physiologic, and metabolic changes that vary between species during pregnancy and nursing of infants.

At a minimum, EPA should explicitly discuss, with supporting evidence, the implications of the absence of a pregnancy model in the PBPK model with regard to deriving points of departure and ultimately estimating risk. As part of this discussion, EPA should describe how the protection of vulnerable populations, including the developing fetus, is ensured given EPA's reliance on the existing PBPK model that does not incorporate a pregnancy component.

### **C. EPA's weight of evidence approach for congenital heart defects raises questions.**

#### *i. EPA's weight of evidence criteria raises concerns.*

In Appendix G.2 (p. 611), EPA notes its selection of the Risk Assessment Forum's Weight of Evidence in Ecological Assessment approach to apply to the evidence base for congenital heart defects. EPA uses applies this structured approach only for the congenital heart defect endpoint, and uses a narrative summary in developing a weight of the scientific evidence for all other endpoints. As discussed in section 8 of our comments, EPA has yet to develop or articulate an approach to evidence integration and as such introduces risks for bias and inconsistency within and across risk evaluations. For the TCE draft risk evaluation, EPA explains it has chosen a particular, structured approach to weight of the scientific evidence for fetal cardiac effects because of "conflicting results of the previous WOE assessments" (p. 223), including a problematic Wikoff et al. 2018 publication (see section 4.D.v.). It then explains that "[a]fter reviewing a sampling of recent literature on systematic approaches to performing weight-of-evidence evaluation, EPA adopted the methodology described in [Weight of Evidence in Ecological Assessment. Risk Assessment Forum. EPA/100/R16/00] which advocates presenting the evidence on a semiquantitative scale...." (p. 223). EPA's explanation for the selection of this particular methodology is virtually non-existent and raises many questions including whether

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<sup>41</sup> National Academies of Sciences, Engineering, and Medicine. 2019. *Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

and when the agency will apply this method in future risk evaluations, and the extent to which EPA considered more prominent GRADE-based structured frameworks for evidence integration used by analogous chemical assessment approaches (i.e., National Toxicology Program OHAT health effects evaluations, UCSF Navigation Guide, EPA IRIS assessments). Setting aside these larger issues, the methodology EPA has chosen raises concerns.

The description of the methodology cites three main areas as the basis for scoring of evidence: reliability (quality), relevance, and strength. EPA highlights the strength criterion as a distinguishing feature of this approach, and further explains in a parenthetical that the strength of a given piece of evidence corresponds to its “magnitude, dose-response, etc.” We are concerned with the inclusion of effect “magnitude” as a criterion for consideration, as “magnitude” could be interpreted either as the fraction of the affected population, or the effect size of the change in a measure of outcome. Either way, an effect with a small “magnitude” either may affect a considerable fraction of the exposed population or could be sufficiently severe to warrant concern. Accordingly, we would advise caution in discounting evidence from well-designed, relevant studies with a small magnitude.

*ii. EPA inappropriately combined exposure routes in its evidence integration for congenital heart defects endpoint*

In the weight of evidence analyses for CHD presented in Appendix G.2, in the section for *in vivo* animal studies, EPA jointly considered the evidence for oral and inhalation studies in animals (pp. 620-621). When considered independently, the oral studies had an integrated area score of (+), whereas the inhalation studies had an integrated area score of (-). Taken together, EPA assigned the *in vivo* studies via all routes a (0), which impacts the overall evidence integration for the endpoint (the quantitative nature of its impact is unclear for this semi-quantitative integration approach). It is not appropriate to consider the oral and inhalation routes together in this approach. Given potential differences in toxicokinetics and metabolism across routes, it is certainly plausible that oral exposures are associated with the endpoint while inhalation exposures are not. With this in mind, it would have been appropriate for EPA to conduct WOE analyses separately by route. Had the agency done this, the *in vivo* animal toxicity studies score would have been higher, which would have likely increased the overall Integrated Area Score and summary score.

**D. EPA’s reliance on immune-related endpoints for its determinations of acute and chronic risk deviates from scientific best practices, defies requirements under the law, and is not sufficiently protective of public health.**

In contrast to previous agency assessments of TCE that characterized the chemical’s risks in whole<sup>42</sup> or in part<sup>43</sup> based on fetal cardiac defects, the most sensitive endpoint, EPA has instead reached based its determinations of acute and chronic unreasonable risk on immune-related endpoints.

Notably, EPA agrees the scientific evidence supports TCE-induced cardiac malformations (p. 225):

Overall, an association between increased congenital cardiac defects and TCE exposure is supported by the weight of the evidence, in agreement with previous EPA analyses (U.S. EPA, 2014b; Makris et al., 2016). Therefore, this endpoint was carried forward for dose-response analysis.

Thus, EPA’s decision to make non-cancer risk determinations based on immune-related endpoint is counter to the preponderance of scientific evidence demonstrating TCE induces fetal cardiac malformations. EPA’s decision to base risk determinations on immune-related endpoints reflects an agency choice at direct odds with decades of scientific policy and practice, statutory requirements to protect potentially exposed and susceptible subpopulations and the agency’s mission to protect human health (see subsections 4.E.i.a. and 4.E.i.d. below).

The rationale EPA provides for making risk determinations based on immune-related endpoints raises significant concerns. In section 3.2.6.4, EPA defends its choice of the selected acute non-cancer endpoint, “mortality due to immunosuppression” as observed in Selgrade and Gilmour (2010), and its selected chronic non-cancer endpoint, “autoimmunity” as observed in Keil et al. (2009), based on its rating of the referenced studies as “High” quality per the TSCA systematic review method, whereas EPA rated the study used in previous agency assessments to derive a

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<sup>42</sup> TSCA Work Plan Chemical Risk Assessment. Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses. 2014. Available at: [https://www.epa.gov/sites/production/files/2014-11/documents/tce\\_opptworkplanchemra\\_final\\_062414.pdf](https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf).

<sup>43</sup> 2011 EPA IRIS Assessment. The IRIS RfD for TCE was derived as the midpoint among candidate RfDs for three other endpoints: decreased thymus weight at  $4.8 \times 10^{-4}$  mg/kg-day (Keil et al., 2009), developmental immunotoxicity at  $3.7 \times 10^{-4}$  mg/kg-day (Peden-Adams et al., 2006), and fetal heart malformations at  $5.1 \times 10^{-4}$  (Johnson et al., 2003). Similarly, the IRIS RfC for TCE was derived as the midpoint among candidate RfCs for two other endpoints: decreased thymus weight at  $1.9 \times 10^{-3}$  mg/m<sup>3</sup> (Keil et al., 2009) and fetal heart malformations at 2.1 mg/m<sup>3</sup> (Johnson et al., 2003).

point of departure (POD) and make risk determinations,<sup>44</sup> Johnson et al. (2003), as “Medium” quality.

However, these ratings are based on a profoundly, and fundamentally, flawed systematic review method that is currently, after long delays on EPA’s part, undergoing peer review by the National Academies of Science, Engineering, and Medicine (NASEM). Those flaws include the lack of any empirical support for the scoring system devised, the use of numerical scores to characterize study quality as a general matter, and the lack of a defined procedure for data integration among others (see section 8 and EDF’s previously submitted comments on the TSCA systematic review method<sup>45</sup>). It is also worth noting that the earlier Dawson et al., 1993 study that reported on two TCE dose groups that were included in the Johnson et al., 2003 study had initially received a rating of High, but that rating was downgraded to Medium based on the study evaluator’s professional judgment.<sup>46</sup>

EPA’s scientifically unsupported and contradictory decision results in EPA relying its risk determinations on risk estimates across various TCE exposure scenarios that are orders of magnitude more lax than those risks estimates associated with the most sensitive endpoint, fetal cardiac malformations. See subsection 4.E.i.b. for further discussion of how EPA’s risk determination choice defies decades of agency policy and practice.

The comments that follow address multiple facets of EPA’s TCE hazard characterization as it relates to fetal cardiac defects, and EPA’s unprecedented and unsupported decision to reach determinations of risk that ultimately leave vulnerable Americans unprotected from the harms arising from TCE exposure.

*i. Weight of the evidence supports TCE-induced cardiac malformations.*

Under TSCA as amended by the Lautenberg Act, EPA is required to apply a weight of the scientific evidence approach to the evaluation of chemical risks. Multiple lines of evidence support the finding that fetal cardiac malformations result from gestational exposure to TCE, including epidemiological evidence, laboratory animal studies, metabolism studies, and mechanistic studies.

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<sup>44</sup> TSCA Work Plan Chemical Risk Assessment. Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses. 2014. Available at: [https://www.epa.gov/sites/production/files/2014-11/documents/tce\\_opptworkplanchemra\\_final\\_062414.pdf](https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf).

<sup>45</sup> EDF Comment on EPA’s Systematic Review, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0077>.

<sup>46</sup> [https://www.epa.gov/sites/production/files/2020-02/documents/14\\_tce-data\\_quality\\_evaluation\\_of\\_human\\_health\\_hazard\\_studies\\_-\\_animal\\_and\\_mechanistic\\_data.pdf](https://www.epa.gov/sites/production/files/2020-02/documents/14_tce-data_quality_evaluation_of_human_health_hazard_studies_-_animal_and_mechanistic_data.pdf) (p. 231).

The 2011 EPA IRIS TCE assessment derived reference dose (RfD) and reference concentration (RfC) values in part based on fetal cardiac malformations.<sup>47,48</sup> Following the IRIS assessment, EPA scientists conducted an additional review of TCE-induced cardiac malformations, in part due to the realization that short-term or peak exposures to TCE gestationally could result in adverse fetal outcomes. This review by Makris et al. was published in a peer-reviewed journal in 2016.<sup>49</sup> As with the IRIS assessment, Makris et al. applied a systematic approach to rigorously identify and evaluate the literature bearing on fetal cardiac defects resulting from gestational exposures to TCE, and applied a weight of the scientific evidence approach in drawing conclusions. The literature search spanned epidemiological, animal, and mechanistic data. Drawing from this broad evidence base, the 2016 review affirmed the earlier IRIS determination that fetal cardiac malformations occur following *in utero* exposure to TCE.

We strongly support EPA's conclusion in the draft risk evaluation that "evidence of a single dominant MOA is not required in order for the data to support a plausible mechanism of TCE-induced congenital heart defects," particularly given that "teratogens may function through a multitude of pathways, often resulting in a constellation of effects" (p. 224). As discussed in the 2014 NAS *Review of EPA's Integrated Risk Information System (IRIS) Process*:<sup>50</sup>

Organizing evidence around mechanism for chemicals on which only some human or animal data are available, however, seems inappropriate. Consider the Food and Drug Administration (FDA) and drug safety. If FDA were required to organize drug safety around mechanism, it would be nearly impossible to regulate many important drugs because the mechanism is often not understood, even for drugs that have been studied extensively. For example, it is known that estrogen plus progestin therapy causes myocardial infarctions on the basis of randomized clinical trials even though the mechanism is not understood (Rossouw et al. 2002). Randomized clinical trials are so successful partly because they bypass the need for mechanistic information and provide an indication of efficacy. Similarly,

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<sup>47</sup> EPA IRIS Assessment for Trichloroethylene. 2011. Available at:

[https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance\\_nmbr=199#tab-1](https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199#tab-1)

<sup>48</sup> It is worth noting that the IRIS RfD for TCE was derived as the midpoint among candidate RfDs for three other endpoints: decreased thymus weight at  $4.8 \times 10^{-4}$  mg/kg-day (Keil et al. 2009), developmental immunotoxicity at  $3.7 \times 10^{-4}$  mg/kg-day (Peden-Adams et al. 2006), and fetal heart malformations at  $5.1 \times 10^{-4}$  (Johnson et al., 2003). Similarly, the IRIS RfC for TCE was derived as the midpoint among candidate RfCs for two other endpoints: decreased thymus weight at  $1.9 \times 10^{-3}$  mg/m<sup>3</sup> (Keil et al., 2009) and fetal heart malformations at 2.1 mg/m<sup>3</sup> (Johnson et al., 2003).

<sup>49</sup> Makris, Susan L. "The systematic review of TCE cardiac defects (Makris et al., 2016)." *Reproductive toxicology (Elmsford, NY)* 71 (2017): 124.

<sup>50</sup> National Research Council. 2014. *Review of EPA's Integrated Risk Information System (IRIS) Process*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/18764>.

epidemiologic studies that identify unintended effects are often credible because explanations of an observed association other than a causal effect are implausible. For example, the associations between statins and muscle damage and between thalidomide and birth defects are widely accepted as causal; mechanistic information played a minor role in the determination, if any. The history of science is replete with solid causal conclusions in advance of solid mechanistic understanding.

While defined MOAs are not required for hazard identification, it should be noted that Makris et al. developed a preliminary Adverse Outcome Pathway (AOP) providing biological support for TCE-induced cardiac effects, specifically valvulo-septal defects, following developmental exposure. Comparing knockout mice with abnormalities in epithelial-mesenchymal transition (EMT) – a key process underpinning valvulo-septal morphogenesis – yielded identification of phenotypes similar to those observed in avian TCE studies examining developmental exposure. Makris et al. indicate that additional mechanistic support for EMT disruption in TCE-induced cardiac malformation is provided by studies that reveal TCE associated “inhibition of cell-cell separation and mesenchymal formation, alterations in mesenchymal cell migration, and alterations in endocardial proliferation patterns.”<sup>51</sup>

Based on their review of the evidence base regarding TCE-induced fetal cardiac malformations, Makris et al. conclude:

Despite the recognized uncertainties and limitations in the TCE database, the evidence supports a conclusion that TCE has the potential to cause cardiac defects in humans when exposure occurs at sufficient dose during a sensitive period of fetal development. This conclusion is warranted by the data that demonstrate or suggest a potential hazard to cardiac development, including epidemiological studies, developmental toxicology studies in rodents with TCE and its metabolites (DCA and TCA), avian *in ovo* studies, *in vitro* assays, and mechanistic data that form the basis of a preliminary conceptual model of an AOP for valvulo-septal defects result from TCE exposures. Limitations within the database that increase the uncertainties regarding this conclusion are acknowledged.

Support for TCE-induced fetal cardiac malformations based on weight of evidence considerations has also been provided by:

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<sup>51</sup> Makris, Susan L., et al. "A systematic evaluation of the potential effects of trichloroethylene exposure on cardiac development." *Reproductive Toxicology* 65 (2016): 321-358.

- the EPA Science Advisory Board (SAB) in its review of the IRIS TCE toxicological review,<sup>52</sup>
- an EPA TCE Developmental Cardiac Toxicity Assessment Update (“Update”) following the publication of the IRIS toxicological review,<sup>53</sup> and
- EPA’s response for a Request for Correction submitted by the Halogenated Solvents Industry Alliance regarding raising concerns regarding the agency’s reliance on Johnson 2003.<sup>54</sup>

For example, the EPA SAB noted in its review, “The Panel found that the draft document adequately synthesizes the available scientific information to support a conclusion that TCE poses a potential human health hazard for non-cancer toxicity, including effects on...the developing fetus.”<sup>55</sup>

The Update stated:

The majority of the team members agreed that the overall evidence in the TCE database supports a conclusion that TCE is likely to cause cardiac defects at sufficient doses when exposure occurs during a sensitive period of fetal development. This conclusion was based upon the data that demonstrate or suggest a potential hazard to cardiac development, including epidemiology studies, developmental toxicology studies in rodents with TCE and its metabolites (DCA and TCA), avian *in ovo* studies, *in vitro* assays, and mechanistic data that form the basis of a proposed AOP.<sup>56</sup>

DeSesso et al. 2019 singularly focuses on refuting the findings of Johnson et al. 2003 to argue that developmental exposure to TCE does not induce cardiac malformations, noting that:

TCE is also listed as a high priority chemical for evaluating the human health risks to workers and the general population under the...Frank F. Lautenberg Chemical Safety for the 21st Century Act. EPA is required by Congress to

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<sup>52</sup>

[https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/B73D5D39A8F184BD85257817004A1988/\\$File/EPA-SAB-11-002-unsigned.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/B73D5D39A8F184BD85257817004A1988/$File/EPA-SAB-11-002-unsigned.pdf) p. ii.

<sup>53</sup> <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2012-0723-0045>.

<sup>54</sup> <https://www.epa.gov/sites/production/files/2015-10/documents/14001-response.pdf>.

<sup>55</sup>

[https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/B73D5D39A8F184BD85257817004A1988/\\$File/EPA-SAB-11-002-unsigned.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/B73D5D39A8F184BD85257817004A1988/$File/EPA-SAB-11-002-unsigned.pdf), p. ii.

<sup>56</sup> <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2012-0723-0045>, p. 7.

complete this assessment by the end of 2019. Hence, there is an important need to resolve the reproducibility of the Johnson et al. (2003) study.<sup>57</sup>

This narrow focus is incredibly myopic, and at odds with TSCA and EPA's own regulation that requires that the agency apply a weight of the scientific evidence approach to evaluating chemical risks.<sup>58</sup> Specifically, EPA's risk evaluation rule states that "[Weight of the scientific evidence] starts with assembling the relevant information, evaluating the information for quality and relevance, and synthesizing and integrating the different lines of evidence to support conclusions."<sup>59</sup> The publication by DeSesso et al. is far from anything resembling that would meet EPA's requirements under TSCA to comprehensively evaluate the evidence regarding TCE and fetal cardiac malformations.

*ii. Additional mechanistic support for TCE-induced fetal cardiac malformations*

EPA appropriately conducted an additional literature search to supplement the database of information on congenital heart malformations (p. 223). Yet, in addition to the Harris et al. 2018 mechanistic study identified by the Agency, there are other relevant studies supporting a mechanistic linkage between TCE and developmental cardiac malformations that EPA should have considered and must consider prior to finalizing the TCE risk evaluation:

Caldwell, Patricia T., et al. "Gene expression profiling in the fetal cardiac tissue after folate and low-dose trichloroethylene exposure." *Birth Defects Research Part A: Clinical and Molecular Teratology* 88.2 (2010): 111-127.

Selmin O.I., Makwana O., Runyan R.B. (2014) Environmental Sensitivity to Trichloroethylene (TCE) in the Developing Heart. In: Gilbert K., Blossom S. (eds) *Trichloroethylene: Toxicity and Health Risks. Molecular and Integrative Toxicology.* Springer, London.

Jin, Hongmei, et al. "AHR-mediated oxidative stress contributes to the cardiac developmental toxicity of trichloroethylene in zebrafish embryos." *Journal of hazardous materials* 385 (2020): 121521.

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<sup>57</sup> DeSesso, John M., et al. "Trichloroethylene in drinking water throughout gestation did not produce congenital heart defects in Sprague Dawley rats." *Birth defects research* 111.16 (2019): 1217-1233.

<sup>58</sup> <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0654-0108>.

<sup>59</sup> Ibid.

iii. EPA has repeatedly examined TCE-induced cardiac malformations and the use of Johnson et al. 2003 specifically for determining TCE hazard and risk, concluding the evidence to be scientifically robust and Johnson et al. 2003 to be appropriate for the derivation of toxicity values and risk estimates.

In 2014, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) conducted a Work Plan Chemical Risk Assessment of TCE focused on the chemical's use in degreasing, spot cleaning, and arts and crafts. The assessment relied on Johnson et al. 2003 to derive toxicity values for the fetal cardiac malformation endpoint. EPA IRIS also used Johnson et al. 2003 to support derivation of a reference dose (RfD) and reference concentration (RfC) for TCE.

Industry groups have repeatedly challenged EPA's use of Johnson et al. 2003, pointing to certain limitations in study design and reporting, several of which were addressed in errata published since the original publication. Limitations of the Johnson study have been repeatedly discussed and addressed by the Agency in a number of TCE assessment related documents:

- IRIS Toxicological Review of TCE (2011)<sup>60</sup>
- TCE Developmental Cardiac Toxicity Assessment Update ("Update")<sup>61</sup> (2014)
- TCE work plan risk assessment (2014)<sup>62</sup>
- TCE work plan risk assessment response to comments (2014)<sup>63</sup>
- Response to HSIA response for correction (2015)<sup>64</sup>
- Response to HSIA response for correction (2016)<sup>65</sup>
- Response to HSIA request for reconsideration (2016)<sup>66</sup>

Throughout the course of developing prior TCE assessments, EPA extensively and repeatedly reviewed, discussed, and resolved limitations associated with the Johnson et al. 2003 study, in each case concluding that that the study is sufficient for hazard identification and dose-response analysis. For example, in the Update, the Agency notes:

On the whole, a majority of the team members agreed that Johnson et al. (2003) is suitable for use in deriving a point of departure. The study has an appropriate design for dose-response analysis in terms of route, duration, and number dose

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<sup>60</sup> <https://www.epa.gov/iris/supporting-documents-trichloroethylene>.

<sup>61</sup> <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2012-0723-0045>.

<sup>62</sup> [https://www.epa.gov/sites/production/files/2014-11/documents/tce\\_opptworkplanchemra\\_final\\_062414.pdf](https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf).

<sup>63</sup> <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2012-0723-0039>.

<sup>64</sup> <https://www.epa.gov/sites/production/files/2015-10/documents/14001-response.pdf>.

<sup>65</sup> [https://www.epa.gov/sites/production/files/2016-12/documents/epa\\_response\\_to\\_rfc\\_16001.pdf](https://www.epa.gov/sites/production/files/2016-12/documents/epa_response_to_rfc_16001.pdf).

<sup>66</sup> <https://www.epa.gov/quality/epa-response-rfr-14001a-issued-02262016-0>.

groups. Additionally, this judgment also took into consideration the strengths and limitations of the study and uncertainties identified in the weight of evidence analysis. Additional support was derived from the finding of a robust, statistically significant dose-response relationships [*sic*] not only for the dataset as a whole, but also for various subsets of the dataset. Although some concern was raised regarding the plateau in the Johnson et al. (2003) response, its biological plausibility could not be ruled out based on examination of historical developmental toxicity datasets.<sup>67</sup>

The earlier peer review by EPA's Scientific Advisory Board of the IRIS TCE toxicological review drew a similar conclusion:

The report [IRIS Assessment] explains logically why the Johnson et al. (2003) study was used to derive some reference points. Some recent publications confirm and reinforce the results obtained in the Johnson et al. (2003) study and could be cited to make a stronger argument.<sup>68</sup>

In sum, the science issues associated with the 2003 Johnson study have been amply vetted and peer-reviewed and should be considered resolved. See Appendix 1 for a brief history of peer reviews associated with previous EPA assessments of TCE: EPA 2014 TCE work plan assessment and 2011 IRIS Toxicological Review of TCE.

Finally, it is important to recognize that Johnson et al. 2003 is wholly consistent with the findings of many other studies—including human, animal, and mechanistic studies—that also indicate fetal cardiac effects resulting from TCE exposure; these were extensively reviewed by Makris et al. 2016, and recently revisited by Runyen et al. 2019. These findings are also addressed in other areas of section 4 of these comments. The Agency must continue to assess and determine risks for this endpoint in light of the entire body of scientific evidence.

*iv. DeSesso et al. 2019 does not negate the body of evidence supporting TCE-induced cardiac malformations, and itself presents methodological shortcoming and unsupported conclusions.*

DeSesso et al. 2019, a publication based on the Charles River Laboratories (2019) study sponsored by the American Chemistry Council and the Halogenated Solvents Industry Alliance, attempts to refute the evidence for TCE-induced fetal cardiac malformations by critiquing

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<sup>67</sup> <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2012-0723-0045>.

<sup>68</sup> [https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/B73D5D39A8F184BD85257817004A1988/\\$File/EPA-SAB-11-002-unsigned.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/B73D5D39A8F184BD85257817004A1988/$File/EPA-SAB-11-002-unsigned.pdf).

Johnson et al. 2003. Specifically, DeSesso et al. 2019 reviews the Charles River Laboratories rodent developmental toxicity study of TCE delivered via drinking water—the same general study design as Johnson et al. 2003—where the authors report that no fetal cardiac effects were observed, and also critiques a single *in ovo* study by Boyer, Finch, and Runyan 2000.

Beyond ignoring the much broader and extensive literature dealing with TCE-induced fetal cardiac malformations, the Charles River Laboratories study has multiple shortcomings such that it cannot be used as a basis to negate the findings of Johnson et al. 2003. EPA’s draft risk evaluation appropriately notes:

While the results of the Charles River study (2019) results appear to contradict the results observed by (Johnson et al., 2003) and (Dawson et al., 1993), EPA concludes that that Charles River study methodology was likely of reduced sensitivity and therefore does not entirely replicate the study conditions of those earlier studies. (p. 222)

It is also worth emphasizing that while DeSesso et al. states that no fetal cardiac effects were observed, the Charles River Laboratories study (2019) did in fact identify cardiac effects; the study authors ignore them by erroneously, deeming the observed effects to be insignificant (see subsection 4.D.iv.c.).

- a. *The heart dissection method used in DeSesso et al. 2019 is insufficiently sensitive to detect cardiac malformations.*

With regard to DeSesso et al. 2019, the draft risk evaluation notes:

...the methodology and positive control data indicate that the Charles River study (2019) was primarily focused on ventricular septal defects (VSDs) and therefore did not sufficiently examine the complete range of potential cardiac defects. The Johnson study (2003) specifically described assessment of valves and observed both valve and atrial defects using their laboratory dissection and examination methodology. In contrast, while the Stuckhardt and Poppe dissection method (1984) used by the Charles River study did not report valve defects in any TCE group or the RA positive control even though many other published reports have identified valve defects following administration of TCE or RA. Additionally, the Stuckhardt and Poppe method (1984) does not include examination of the heart for atrial septal defects, and the Charles River study did not report any atrial septal defects in either the RA positive control group or the TCE groups. In fact, the Charles River study (2019) observed a similar percentage of VSDs as (Johnson et al. 2003)...As further indication of the potentially limited sensitivity of (Charles Rivers Laboratories, 2019), the defects observed from exposure to the

retinoic acid (RA) positive control were also somewhat limited compared to the broader RA literature (which did identify atrial septal defects). (pp. 222-223)

As recognized by EPA, the concerns about the sensitivity of the Charles River Laboratories study mean both that the study's assertions of the absence of fetal cardiac defects following TCE exposure are not supported, and that the study cannot be used to negate the findings of Johnson et al. 2003, which has been extensively and repeatedly peer-reviewed by EPA and peer review panels such as the Agency's Scientific Advisory Board.

*b. DeSesso et al. 2019's differential administration of test substance and positive control contradicts the applicable test guidelines.*

The DeSesso et al. study was purportedly conducted in accordance with the OECD Test Guideline 414,<sup>69</sup> among others. This OECD Test Guideline specifically states that “[a]nimals in the control group(s) should be handled in an identical manner to test group animals” (p. 4). However, in DeSesso et al., retinoic acid (the positive control) was administered in a completely different manner than was TCE. Retinoic acid was delivered by daily oral gavage, while TCE was administered through drinking water. Furthermore, retinoic acid was only administered during gestational days (GD) 6-15, while TCE was administered during GD 1-21. These differences introduce call into question the experimental design and could compromise the validity and utility of the study's positive control.

*c. Relevance of all ventricular septal defects (VSDs)*

DeSesso et al. attempt to downplay the significance of the small VSDs (<1 mm) that were observed in their study, claiming that “small VSDs which close spontaneously...should be considered normal developmental delay.”<sup>70</sup> In Appendix G, EPA appropriately points out concerns with regard to this statement, namely that (p. 609):

[t]his claim is confounding and internally inconsistent however, because the vast majority (92%) of VSDs observed in the RA-treated positive control group were also <1 mm. If VSDs <1 mm are truly non-adverse, then this positive control data provides additional indication that the study is insufficiently sensitive for detecting adverse cardiac effects,

Moreover, the claim that small VSDs are not adverse is not supported by the epidemiological literature on congenital heart malformations. First, recent studies indicate that even small VSDs

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<sup>69</sup> [https://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study\\_9789264070820-en](https://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study_9789264070820-en).

<sup>70</sup> DeSesso, John M., et al. "Trichloroethylene in drinking water throughout gestation did not produce congenital heart defects in Sprague Dawley rats." *Birth defects research* 111.16 (2019): 1217-1233.

that do not require surgery can result in significant morbidity leading to medical complications over the course of life.<sup>71,72,73,74,75</sup> As stated by one group of study authors, the “data show that the clinical course of isolated, small restrictive VSDs cannot be assumed to be benign.”<sup>76</sup> More broadly, these conclusions regarding the potential for lifelong cardiac complications are relevant for numerous categories/types of lower-complexity congenital heart disease.<sup>77</sup> Furthermore, it should also be noted that growing evidence indicates that individuals who undergo surgery for VSD closure experience significant long-term complications, particularly related to reduced cardiac function.<sup>78,79,80,81</sup>

Overall, the evidence does not support DeSesso et al.’s assertion that small VSDs do not have clinical significance. Data clearly indicate that even small cardiac malformations can lead to lifelong - and potentially costly - morbidity.

*d. Flaws in DeSesso et al. 2019 highlighted by a letter to the editor by Runyan et al 2019*

In response to DeSesso et al. 2019, Runyan et al. – experts in developmental toxicology and cardiac malformations – published a letter to the editor highlighting the following:

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<sup>71</sup> Goldberg, Jason F. "Long-term Follow-up of “Simple” Lesions—Atrial Septal Defect, Ventricular Septal Defect, and Coarctation of the Aorta." *Congenital heart disease* 10.5 (2015): 466-474.

<sup>72</sup> Gabriel HM, Heger M, Innerhofer P, et al. Long-term outcome of patients with ventricular septal defect considered not to require surgical closure during childhood. *J Am Coll Cardiol.* 2002;39:1066–1071.

<sup>73</sup> Karonis, Theodoros, et al. "Clinical course and potential complications of small ventricular septal defects in adulthood: Late development of left ventricular dysfunction justifies lifelong care." *International journal of cardiology* 208 (2016): 102-106.

<sup>74</sup> Neumayer, U., S. Stone, and J. Somerville. "Small ventricular septal defects in adults." *European heart journal* 19.10 (1998): 1573-1582.

<sup>75</sup> Soufflet, Veerle, et al. "Behavior of unrepaired perimembranous ventricular septal defect in young adults." *The American journal of cardiology* 105.3 (2010): 404-407.

<sup>76</sup> Karonis et al, 2016

<sup>77</sup> Saha, Priyanka, et al. "Substantial Cardiovascular Morbidity in Adults With Lower-Complexity Congenital Heart Disease." *Circulation* 139.16 (2019): 1889-1899.

<sup>78</sup> Goldberg, 2015.

<sup>79</sup> Menting ME, Cuypers JA, Opić P, et al. The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure. *J Am Coll Cardiol.* 2015;65:1941–1951.

<sup>80</sup> Heiberg J, Petersen AK, Laustsen S, Hjortdal VE. Abnormal ventilatory response to exercise in young adults operated for ventricular septal defect in early childhood: a long-term follow-up. *Int J Cardiol.* 2015;194:2–6.

<sup>81</sup> Nederend, Ineke, et al. "Long-term follow-up after ventricular septal defect repair in children: cardiac autonomic control, cardiac function and exercise capacity." *European Journal of Cardio-Thoracic Surgery* 53.5 (2017): 1082-1088.

Since Johnson et al. (2003), we have gained substantial understanding of cardiac morphogenesis and the critical contributions of both function and gene expression. Measures of these latter elements provide nuanced understanding of how toxicants disturb cardiac structure and functionality. DeSesso et al. utilizes a static assessment methodology that captures only a subset of dysmorphologies and does not evaluate actual function. We argue that their data is insufficient to overcome a substantial literature showing the sensitivity of the developing heart to environmentally relevant TCE exposures. Their conclusion that ingestion of TCE in drinking water at less than 1,000 ppm does not cause heart defects is not supported by their data.<sup>82</sup>

The authors further indicate that the Johnson et al. 2003 itself likely missed cardiac-related effects of TCE at low levels of exposure, attributed to extensive evidence of non-monotonicity at levels of exposure below 1,000 ppm:

The study [DeSesso et al., 2019] design ignores the many studies published in the last 18 years that show TCE toxicity at exposures lower than 1,000 ppm, as well as evidence that TCE exhibits nonmonotonic effects. Our laboratories have shown that low level exposures in the 10–100 ppb range inhibit developmental mechanisms, alter gene transcription and produce changes in cardiac output. These effects occur with exposures below the range tested by DeSesso et al.<sup>83</sup>

Table 1 of the authors' letter, which is provided as Appendix 3 to our comments, illustrates the extensive study database demonstrating effects of TCE below 1000 ppm.

Overall, the Runyan et al. 2019 letter lends further support to an already significant body of evidence that TCE exposure causes fetal cardiac malformations, likely at levels of exposure below even what Johnson et al. 2003 suggests.

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<sup>82</sup> Runyan, R.B., Selmin, O.I., Smith, S.M. and Freeman, J.L. (2019), Letter to the Editor. Birth Defects Research, 111: 1234-1236. doi:[10.1002/bdr2.1573](https://doi.org/10.1002/bdr2.1573).

<sup>83</sup> Ibid.

*e. Conflict of interest in DeSesso et al.*

Given the well-documented association between research sponsorship and study findings,<sup>84,85,86</sup> it should be noted that the DeSesso et al. 2019 study was commissioned and supported by the Halogenated Solvents Industry Alliance (HSIA) and the American Chemistry Council (ACC).<sup>87</sup> These groups represent companies that have direct and substantial financial interests in the continued production and use of TCE as well as with respect to potential liability associated with releases and exposures to TCE, including from contaminated sites. Risk of bias from conflict of interest is an important consideration in systematic review of the environmental health field and it should be - but has not been - considered by OPPT.<sup>88</sup>

*v. EPA missed key flaws in Wikoff et al., 2018 that should have reduced its confidence in the conclusions of that review*

EPA makes references to the conflicting results of two prior WOE analyses, (Makris et al., 2016 and Wikoff et al., 2018) as a rationale for conducting a new WOE analysis in support of the DRE. Our examination of the Wikoff et al., 2018 review identified numerous, significant flaws that likely adversely impact confidence in its conclusions.

*a. Creation of “sub-domains”*

Wikoff et al., 2018 adapts the Office of Health Assessment and Translation (OHAT) Risk of Bias (RoB) rating tool for human and animal studies to assess the internal validity of experimental animal and human evidence linking maternal exposure to TCE to fetal congenital heart defects. The studies examined by the authors include those previously examined in Makris et al. (2016) and additional studies published after Makris’ review window (2010 – 2015) and additional studies they identified through reference lists from existing papers and reviews. The authors state that, following guidance presented in the OHAT handbook, they have modified the OHAT framework to tailor it to the specific research hypothesis under study. Specifically,

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<sup>84</sup> Lee Friedman & Michael Friedman, Financial conflicts of interest and study results in environmental and occupational health research, 58:3 J. OF OCCUPATIONAL & ENVTL. MEDICINE 238-247 (2016).

<sup>85</sup> Lisa Bero, et al., The relationship between study sponsorship, risks of bias, and research outcomes in atrazine exposure studies conducted in non-human animals: Systematic review and meta-analysis, 92 ENV’T INT’L 597-604 (2016)

<sup>86</sup> Jenny White & Lisa Bero, Corporate manipulation of research: strategies are similar across five industries, 21 STAN. L. & POL’Y REV. 105 (2010)

<sup>87</sup> DeSesso et al., 2019

<sup>88</sup> Tracey Woodruff, et al., An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences, 30:5 HEALTH AFFAIRS 931-937 (2011); see also EDF comments on TSCA systematic review, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0077>.

Wikoff et al. took some of the 11 research questions/domains from OHAT and created “subdomains” that split out the combined criteria into multiple, separate considerations. For example, in OHAT, Question 1, “[w]as administered dose or exposure level adequately randomized?”, was broken into two separate subdomains, Question 1a (“Adequate randomization of animals to control or exposure/dose groups”) and Question 1b (“Were all study groups (control and exposed) investigated concurrently?”). While both concepts are jointly considered in OHAT guidance, separating them into multiple questions creates additional opportunities to highlight shortcomings of individual studies. It is not clear whether the subdomains are quantitatively considered equivalent to domains (this is not clearly described in the study), but the visual effect on RoB heatmaps is that studies that perform poorly on individual subdomains appear to be of even lower quality than they would be if subdomains were retained as single domains per the OHAT RoB rating tool.

It is also worth examining the choices made with respect to deconstruction of domains into subdomains. Curiously, the Johnson et al. (2003) study, which has been the study used by EPA for quantitative dose-response assessment (and was defended in Makris et al. [2016] as the best choice for this purpose) performs especially poorly according to the rating scheme fabricated by Wikoff and the associated heat maps. It would seem that Wikoff worked backwards from shortcomings in conduct/presentation of the Johnson (2003) to put more emphasis on the elements of the OHAT framework that would devalue that study and cause it to be discarded.

*b. Problems with “key” criteria and their application to the Johnson et al. 2003 study*

Key Criterion 5b:<sup>89</sup> For the Johnson study, Wikoff selects a bias rating that means: “Probably High - indirect evidence that non-treatment-related experimental conditions were not comparable between study groups.” There is no evidence presented to support this rating. The authors in the 2005 erratum to the Johnson study say, “The control “sets” were statistically analyzed comparing the data to each other before being combined. The authors opine that the control values were statistically consistent across and throughout all the treatment groups. Using the control data in a cumulative manner increased the generalizability of the data, which purports to demonstrate the background rate and variability around rate estimates.”<sup>90</sup>

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<sup>89</sup> Criterion 5b in Wikoff et al. is as follows: “Question 5b—Were non-treatment-related experimental conditions the same for all study groups (control and exposed)?” (p. 127).

<sup>90</sup> Johnson, Paula D., et al. "Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat." *Environmental health perspectives* 111.3 (2003): 289-292. Erratum-ibid: <https://ehp.niehs.nih.gov/doi/10.1289/ehp.113-1253738>.

Key Criterion 9a:<sup>91</sup> Wikoff et al. make a determination regarding the acceptable methods for assessment of CHD outcomes:

Given the minute size of the fetal heart in rodents and other small animal species, and the sensitivity of this organ tissue, CHDs have been commonly identified by using 1 of 2 common and acceptable fetal dissection techniques [reviewed in Tyl and Marr<sup>27</sup>]: the fresh in situ microdissection technique<sup>28,29</sup> and the fixation, serial sectioning technique.<sup>30</sup>

The authors state that use of these specific methods results in a low risk of bias. Johnson et al. 2003 applied a different cardiac evaluation method and therefore received a “probably high” risk of bias rating for this criterion. However, in the draft risk evaluation, Table Apx G-5 (p. 603-604), EPA presents a comparison of the types of cardiac malformations observed under the methods employed by each study, noting that the Johnson study was capable of detecting a variety of septal and valve defects, as well as atrial, ventricular, and other miscellaneous abnormalities (many of which were not observable using the methods employed by the 2019 Charles River study). EPA further elaborates in Appendix G.1.2.3 key differences in the dissection methods between Johnson et al. 2003 and the 2019 Charles River study that would lead to superior sensitivity of Johnson et al. 2003 in the detection of cardiac malformations (p. 607-609). On these bases, it appears entirely unreasonable that Wikoff et al. 2018 rated Johnson et al. 2003 as probably high bias for outcome assessment.

*c. Risk of bias tables not available*

The completed risk of bias tables were not available from the Wikoff study. This lack of transparency prevents EPA and the public from examining the bases and justifications for the specific ratings for each study.

**E. EPA should include fetal cardiac malformations in the assessment of acute risks from TCE exposure.**

EPA appropriately recognizes that developmental studies are relevant for evaluating acute exposure scenarios. EPA notes:

Although developmental studies typically involve multiple exposures, they are considered relevant for evaluating single exposures because evidence indicates that certain developmental effects may result from a single exposure during a critical window of development (Davis et al., 2009; Van Raaij et al., 2003). This is consistent with EPA’s Guidelines for Reproductive Toxicity Risk Assessment

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<sup>91</sup> Criterion 9a in Wikoff et al. is as follows: “Question 9a—Is there confidence in the outcome assessment method?”

(U.S. EPA, 1996) and Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), which state that repeated exposure is not a necessary prerequisite for the manifestation of developmental toxicity. This is a health protective assumption. (p. 221)

In its determinations of acute risks resulting from TCE exposure, however, EPA chose to rely on its margin of exposures (MOE) values based on immunosuppression as measured by mortality: “Mortality was selected as the most statistically sensitive endpoint due to a larger numbers of mice per exposure group and more dose groups....” (p. 231).

EPA’s decision is flawed, and contradicts long-standing agency policy and previous EPA assessments of TCE that require basing risk assessment and protection on the most sensitive endpoint.

As described in EPA 2014 TCE work plan assessment and in the TSCA section 6 proposed rules for the use of TCE in vapor degreasing, aerosol degreasing, and in spot cleaning in dry cleaning facilities, the agency relied on developmental endpoints for assessing and addressing the health risks of TCE resulting from acute exposure.

For example, EPA states in section 2.7.2 of the 2014 TCE Work Plan Chemical Risk Assessment:

The acute inhalation risk assessment used developmental toxicity data to evaluate the acute risks for the TSCA TCE use scenarios. As indicated previously, EPA’s policy supports the use of developmental studies to evaluate the risks of acute exposures. This policy is based on the presumption that a single exposure of a chemical at a critical window of fetal development, as in the case of cardiac development, may produce adverse developmental effects (EPA, 1991).<sup>92</sup>

EPA elaborated extensively on the use of developmental toxicity to assess acute risks of TCE in its response to comments associated with the 2014 Work Plan Chemical Risk Assessment for TCE. Specifically, the agency stated:

EPA/OPPT used developmental toxicity data to evaluate the non-cancer risks of acute exposures based on EPA’s long standing policy that a single exposure within a critical window of development may induce developmental effects, as discussed in the EPA’s Guidelines for Developmental Toxicity Risk Assessment (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162>). EPA/OPPT

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<sup>92</sup> [https://www.epa.gov/sites/production/files/2015-09/documents/tce\\_opptworkplanchemra\\_final\\_062414.pdf](https://www.epa.gov/sites/production/files/2015-09/documents/tce_opptworkplanchemra_final_062414.pdf), p. 104.

acknowledges that this is a health-protective policy that may overestimate the acute risks.

Developmental effects, including fetal cardiac defects, may occur following maternal exposure to TCE. Chick embryo and oral developmental studies, including those reported by the Johnson et al. studies (see list of references below), have reported cardiac malformations after exposure to TCE. The incidence of congenital cardiac malformation has been replicated in several studies from the same laboratory group and has been shown to be TCE-related. Moreover, studies with TCE metabolites have also induced cardiac defects in developmental oral toxicity studies.

A recent erratum (Johnson, 2014) and subsequent evaluation of the developmental toxicity data reaffirmed that the Johnson et al. studies are adequate to use in hazard identification and dose-response assessment (Appendix N). As explained in the TCE IRIS assessment, while the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with human, animal and mechanistic evidence. A summary of the weight of evidence supporting TCE-related fetal cardiac defects is provided in section 2.6.2.3.6 and Appendix N of the final TCE OPPT risk assessment. The comprehensive WOE evaluation of the developmental toxicity data, including fetal cardiac teratogenesis, is discussed in the TCE IRIS assessment and expanded in this assessment (Appendix N).<sup>93</sup>

Further, as elaborated on in section 4.D.iii. of these comments, EPA has previously determined and explained that Johnson et al. 2003 is appropriate for deriving a point of departure. In this draft risk evaluation, however, rather than abide by health-protective agency policy and precedents from previous agency assessments—which have undergone extensive peer review (see Appendix 1)—the agency has decided to rely on immunosuppression as measured by death in mice as a basis for its determinations for acute risks resulting from TCE exposure. The effect of this decision to lower the risk estimates by several orders of magnitude across multiple conditions of use.

EPA's decision not to take a health-protective approach to assessing acute TCE risks is at odds with TSCA's requirement to protect potentially exposed or susceptible subpopulations, which explicitly include pregnant women and children.

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<sup>93</sup> [https://www.epa.gov/sites/production/files/2015-09/documents/tce\\_response\\_to\\_comments\\_final\\_062414.pdf](https://www.epa.gov/sites/production/files/2015-09/documents/tce_response_to_comments_final_062414.pdf), p. 17-18.

- i. *Scientific, policy and legal arguments against EPA’s decision not to rely on fetal cardiac effects*
  - a. *TSCA’s requirement that EPA assess risks to susceptible subpopulations demands that EPA base its risk determinations on the endpoint—congenital health defects—that specifically impacts pregnant women, infants, and children.*

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.

In turn, TSCA section 3(12) defines “potentially exposed or susceptible subpopulation” as (emphases added):

a group of individuals within the general population identified by the Administrator who, due to either *greater susceptibility* or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as *infants, children, pregnant women, workers, or the elderly*.

EPA acknowledges that “congenital heart defects were the most sensitive endpoint for TCE” (p. 377; Table 4-5 on p. 280), and this endpoint is directly relevant to the potentially exposed or susceptible subpopulations of pregnant women, infants, and children identified under TSCA. Yet EPA fails to rely on this endpoint in its risk determinations and instead relies on a different, far less sensitive endpoint that is not the most relevant to those subpopulations. In making this switch in endpoints, EPA is not only making risk determinations based on a far more lax risk benchmark; it is also failing to carry out its mandate under TSCA section 6(b)(4)(A) to conduct a risk evaluation “to determine whether a chemical substance presents ... *an unreasonable risk to a potentially exposed or susceptible subpopulation.*” EPA cannot adequately identify or protect against risks specific to pregnant women (and their developing fetuses) or infants or children by selecting immune effects as the basis for its risk determinations. EPA must develop risk determinations that address the endpoint—congenital health defects—that specifically impacts pregnant women, infants, and children

- b. *EPA's decision to reach determinations of risk based on immune-related endpoints represents a deeply troubling break with decades of agency scientific policy and practice designed to protect public health.*

In section 5.2, Risk Determinations for TCE, EPA indicates that it has based its determinations of unreasonable risk on immune-related endpoints. Specifically, EPA indicates that it “[i]s relying upon immunosuppression for acute inhalation and dermal exposures, and autoimmunity for chronic inhalation and dermal exposures.” (p. 377) It is worth emphasizing that nothing short of death is the effective endpoint used to derive the point of departure from the immunosuppression study by Selgrade and Gilmour (2010). Based on a comparison of the BMDL<sub>01S</sub> for these endpoints, the result of this choice is a significantly higher increase in the POD, indicating that the selected endpoint is orders of magnitude less sensitive than the CHD endpoint.

With this decision, EPA has chosen not to protect against the most sensitive endpoint, fetal cardiac malformations, for which there is strong scientific support. Indeed, EPA presents a rigorous case for the CHD endpoint throughout the draft risk evaluation, considering multiple lines of evidence that converge into an integrated strength area score of (+) (see Weight of Evidence analysis and summary presented in Appendix G.2). The agency highlights the robust evidence base multiple times throughout the draft risk evaluation:

Overall, an association between increased congenital heart defects and TCE exposure is supported by the weight of the evidence, in agreement with previous EPA analyses (U.S. EPA, 2014b; Makris et al., 2016). Therefore, this endpoint was carried forward to dose-response analysis. (p. 225).

and,

Overall, the database is both reliable and relevant and provides positive overall evidence that TCE may produce cardiac defects in humans (based on positive evidence from epidemiology studies, mixed evidence from animal toxicity studies, and stronger positive evidence from mechanistic studies) (p.621).

In comparison, the overall study database for the immunotoxicity and autoimmunity endpoint is far more limited than for the CHD endpoint. While Selgrade and Gilmour (2010) may have been assigned a high-quality rating as an individual study, this endpoint is orders of magnitude less sensitive and is not supported by the same, rigorous weight of evidence analysis to which the CHD endpoint was subjected.

Furthermore, it is inappropriate to use study quality as the sole basis for endpoint and study selection. Study quality is *an* appropriate consideration of the adequacy of published research to serve as the basis for dose-response analyses. After inappropriate studies are eliminated as

candidates for dose-response analyses, other considerations, such as sensitivity, should form the basis for endpoint selection for dose-response analysis.

Instead of carrying the most sensitive endpoint, fetal cardiac malformations, through to be the basis for its risk determinations, EPA indicates, in defiance of public health protection principles and statutory requirements under TSCA to explicitly protect potentially exposed or susceptible subpopulations, that “[n]either the statute nor the framework rule require that EPA choose the lowest number and EPA believes that public health is best served when EPA relies upon the highest quality information for which EPA has the greatest confidence.” (p. 377) ***In fact, public health is best served when public health is best protected.***

EPA’s decision to ignore strong scientific evidence that indicates TCE induces fetal cardiac malformations at levels of exposure far lower than those associated with the immune-related effects EPA has chosen to use for its risk determinations is not only scientifically unsupported, it is contrary to the agency’s core mission to protect public health. EPA is failing to protect against the most sensitive endpoint, as supported by the weight of the scientific evidence, and is failing to protect a critical susceptible subpopulation: pregnant women and the developing fetus.

EPA’s choice also contradicts previous agency assessments of TCE and existing agency guidance to use the most sensitive endpoint and protect the most sensitive group (emphases added):

- EPA, Guidelines for Developmental Toxicity Risk Assessment: “The risk characterization of an agent should be based on data from the most appropriate species, or, if such information is not available, on the most sensitive species tested. *It should also be based on the most sensitive indicator of toxicity*, whether maternal, paternal, or developmental, when such data are available, and should be considered in relationship to other forms of toxicity.”<sup>94</sup>
- EPA Risk Assessment Task Force, Staff Paper on Risk Assessment Principles and Practices: “Combined with UFs and other upper-bound estimates, *basing cancer and non-cancer risks on the most sensitive animal data* gives reasonable assurance that the potential for harm will not be underestimated, most likely even when some toxicity endpoints have not been evaluated.”<sup>95</sup>

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<sup>94</sup> EPA, Guidelines for Developmental Toxicity Risk Assessment.

[https://www.epa.gov/sites/production/files/2014-11/documents/dev\\_tox.pdf](https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf), p. 48.

<sup>95</sup> EPA. Office of the Science Advisor Staff Paper Risk Assessment Principles and Practices 2004 <https://www.worldcat.org/title/examination-of-epa-risk-assessment-principles-and-practices-staff-paper-prepared-for-the-us-environmental-protection-agency-by-members-of-the-risk-assessment-task-force/oclc/55850621>, pp. 57-58.

- EPA, A Review of the Reference Dose and Reference Concentration Processes: “[T]he ‘critical effect’ is used as the basis for the POD, and various UFs are applied to the dose at the critical effect to derive the RfD or the RfC. *The critical effect is defined as ‘the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases’* (U.S. EPA, 2002c). The underlying assumption is that if the RfD or the RfC is derived to prevent the critical effect from occurring, then no other effects of concern will occur....”<sup>96</sup>
- EPA’s policy on evaluating risk to children: “It is the policy of the U.S. Environmental Protection Agency (EPA) to *consider the risks to infants and children* consistently and explicitly as a part of risk assessments generated during its decision making process, including the setting of standards to protect public health and the environment. To the degree permitted by available data in each case, the Agency will develop a separate assessment of risks to infants and children or state clearly why this is not done - for example, a demonstration that infants and children are not expected to be exposed to the stressor under examination.”<sup>97</sup>

The National Academy of Sciences has also reiterated the need to protect the most sensitive subpopulations and to protect against the most sensitive endpoints:

- National Academy of Sciences, Science and Decisions: Advancing Risk Assessment:
  - “In addition to characterizing the full population at risk, attention should be directed to *vulnerable individuals and subpopulations that may be particularly susceptible* or more highly exposed.”<sup>98</sup>
- NAS, Science and Judgment:
  - “The *most sensitive end point of toxicity* should continue to be used for establishing the reference dose.”<sup>99</sup>
  - “*The critical toxic effect used is the one generally characterized by the lowest NOAEL*. This approach is based on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented.”<sup>100</sup>

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<sup>96</sup> A Review of the Reference Dose and Reference Concentration Processes.

<https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>, p. 4-22.

<sup>97</sup> EPA’s policy on evaluating risk to children. <https://www.epa.gov/children/epas-policy-evaluating-risk-children>, p. 1.

<sup>98</sup> NAS, Science and Decisions: Advancing Risk Assessment.

<https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment>, p. 120.

<sup>99</sup> NAS, Science and Judgment. <https://www.nap.edu/catalog/2125/science-and-judgment-in-risk-assessment>, p. 142.

<sup>100</sup> Ibid. p. 145.

These excerpts represent a non-exhaustive list of direction to agency to protect sensitive subpopulations, and to protect against the most sensitive endpoint. EPA's proposed risk determinations fail on both accounts.

These excerpts also make clear that if EPA protects against the most sensitive endpoint, it will also generally protect against other effects. In contrast, EPA asserts without providing a shred of evidence that "it is expected that addressing risks for these [immune system] effects would address other identified risks." (p. 377). EPA should be ashamed of itself.

*c. Inconsistencies within the draft risk evaluation*

While EPA erroneously prioritizes study quality above all else in selecting the immune endpoints as the basis for its risk determinations for acute and chronic non-cancer risks, the Agency's flawed approach is inconsistent with its decision making in other areas of the assessment. For example, when selecting *between* studies of the same endpoint, EPA seems to have no issue with choosing medium quality studies. For the liver toxicity endpoint (Table 3-8, p. 240), the Agency reviews both High and Medium quality studies and chooses to advance a Medium quality study to represent liver toxicity. Similarly, for the reproductive toxicity endpoint (Table 3-12, p. 248), EPA reviews both High and Medium quality studies and chooses to advance a Medium quality study to represent reproductive toxicity.

These examples clearly indicate that EPA uses study quality in a selective, biased and inconsistent way when it comes to fetal heart defects. Its approach seems intended to allow the Agency to derive less protective hazard values and use them to underestimate risk, to the benefit of industry and allied interests and to the detriment of public health. If the Agency sees fit to advance Medium quality studies within an endpoint, it should be able to do so when selecting acute and chronic non-cancer endpoints, especially when doing so bears directly on the ultimate characterization and determination of risk.

*d. TSCA's requirement that EPA assess risks using the best available science demands that EPA base its risk determinations on congenital health defects.*

The best available science provides evidence of congenital heart defects. EPA itself scored both the Dawson et al. 1993 and Johnson et al. 2003 studies as "a Medium in data quality evaluation," (p. 222) and EPA has repeatedly relied on Medium studies in its draft risk evaluations to date, including this one (see section 4.E.i.c. and 4.F.i.). And in EPA's own words: "Overall, the database is both reliable and relevant and provides positive overall evidence that TCE may produce cardiac defects in humans (based on positive evidence from epidemiology studies, mixed evidence from animal toxicity studies, and stronger positive evidence from mechanistic studies)." (p. 621). To the extent EPA made a scientific finding on congenital heart defects, EPA found that they occur and the evidence indicates that they are the most sensitive endpoint

for TCE. EPA did *not* find that contrary studies on congenital heart defects were stronger or more reliable than the Johnson et al. 2003 study.

Despite these scientific findings on congenital heart defects, EPA chooses to ignore this endpoint in its final analysis, by adopting risk estimates and determinations that do not account for this endpoint. EPA seeks to justify this decision by invoking the “best available science” (p. 377), but in doing so, EPA relies on nonscientific and illogical reasoning. Specifically, EPA states that it has greater confidence in other endpoints—immunosuppression for acute inhalation and dermal exposures, and autoimmunity for chronic inhalation and dermal exposures. (p. 377). EPA then uses this asserted greater confidence to rely on these endpoints for its risk estimates and determination, but nothing about the availability of data in which it says it has greater confidence for these other endpoints undermines the evidence for congenital heart defects. In other words, EPA dismisses the evidence on congenital heart defects by pointing to evidence that has no bearing whatsoever on congenital heart defects.

The “best available science” on congenital heart defects supports that they occur and supports use of the Johnson et al. study. EPA tries to dismiss these findings based on alleged uncertainty, but “[q]uite simply, the [agency] cannot demand a greater level of scientific certainty than has been achieved in the field to date.” *Defenders of Wildlife v. Jewell*, 176 F. Supp. 3d 975, 1003 (D. Mont. 2016); *Survivors v. United States DOI*, 321 F. Supp. 3d 1011, 1040 (N.D. Cal. 2018) (“[W]here superior information is not readily available, the ‘best available science’ requirement of the ESA does not ‘insist on perfection’ and does not require the ‘the best scientific data possible.’”) (quoting *San Luis & Delta-Mendota Water Auth. v. Jewell*, 747 F.3d 581, 602 (9th Cir. 2014)); *NRDC v. Evans*, 364 F. Supp. 2d 1083, 1131 (N. Cal. 2003) (“[An] interpretation of the [best available science] requirement to provide ‘the best scientific data available’ to exclude highly relevant research because its methodology—like most studies—can be criticized effectively eviscerates the requirement to use the best available science and rewrites the standard to perfect science.”).

When the available evidence supports an effect, the agency must give weight to that effect. *See Defenders of Wildlife v. Jewell*, 176 F. Supp. 3d 975, 1003 (D. Mont. 2016). Under the “best available science” standard, the agency “cannot ignore available biological information.” *Conner v. Burford*, 848 F.2d 1441, 1454 (9th Cir. 1988). It also “prohibits [an agency] from disregarding available scientific evidence that is in some way better than the evidence [it] relies on.” *San Luis & Delta-Mendota Water Auth. v. Jewell*, 747 F.3d 581, 602 (9th Cir. 2014) (quoting *Kern County Farm Bureau v. Allen*, 450 F.3d 1072, 1080 (9th Cir. 2006)). It is undisputed that, *with respect to congenital heart defects*, the Johnson et al. study is better evidence than the studies of immunosuppression and autoimmunity, which did not analyze congenital heart defects at all. The problem with EPA’s analysis is that it dismisses the best available science on congenital heart defects by pointing to studies that do not analyze or

consider that endpoint. Even if the studies on immunosuppression and autoimmunity are higher quality, they do not assess congenital heart defects and thus do not speak to this effect.

To draw an analogy to listing species under the Endangered Species Act—another context where the federal government must use the best available science—EPA’s analysis is the equivalent of dismissing habitat destruction despite a finding that habitat is likely to be destroyed simply because the agency has even greater confidence that the species is also threatened by disease. But the logical and scientific approach is to consider both effects, in conjunction, and that is how the agencies tasked with listing species have historically considered such effects. In the context of risk evaluations for chemicals under TSCA, one accounts for multiple effects by selecting the most sensitive endpoint for risk characterization. By addressing the risks for these effects, one also is able to “address other identified risks”—which is allegedly EPA’s goal. (p. 377). In contrast, EPA’s approach of selecting the endpoint with the greatest confidence *does* not “address other identified risks”—it leaves risks from congenital heart defects insufficiently addressed, as indicated by the lower levels of exposure to TCE that cause those defects relative to exposures required to cause the immune effects.

**F. EPA’s chronic non-cancer PODs and related calculations depart from prior assessment decisions and are not sufficiently protective of public health.**

*i. Dismissal of NTP study of kidney toxicity without sufficient justification*

In this draft risk evaluation, EPA selects Maltoni et al. 1986 as the representative study for the kidney toxicity endpoint. This is a departure from the 2014 Work Plan Assessment, in which the NTP 1988 study was selected because it provided the lowest POD. It should be noted that both studies were rated as “Medium” quality in the draft risk evaluation. Yet, as demonstrated in Table 3-9, selecting the Maltoni et al. 1986 study results in an HEC<sub>99</sub> that is nearly five times higher than the HEC<sub>99</sub> derived from the NTP study (Maltoni et al. HEC<sub>99</sub> = 0.025 ppm; NTP HEC<sub>99</sub> = 0.0056 ppm).

EPA seeks to justify this decision because the “elevated doses in (NTP, 1988) resulted in massive nephrotoxicity and introduce large uncertainty in BMD modeling the effects at low doses well below the tested doses with a BMR well below the observed effect incidence in the study” (p. 242). These issues with the NTP 1988 study were directly addressed in the 2011 IRIS assessment and deemed not to represent a concern sufficient to warrant not relying on the NTP study: “This BMR required substantial extrapolation below the observed responses (about 60%); however, the response level seemed warranted for this type of effect and the ratio of the BMD to

the BMDL was not large (1.56).”<sup>101</sup> Furthermore, the 2011 IRIS assessment highlights that the “effect observed in NTP (1988) is more severe.”<sup>102</sup>

Therefore, given that 1) the NTP study provides the *lowest* HEC<sub>99</sub> on the *most severe* kidney toxicity endpoint and 2) modeling challenges did not present concerns in prior assessments, EPA should select the POD from the NTP 1988 study rather than the Maltoni et al. 1986 study to represent the kidney toxicity endpoint.

*ii. Dismissal of key immunotoxicity endpoint without sufficient justification*

In another departure from the 2014 Work Plan Assessment, the Agency decided not to consider decreased thymus weight and cellularity (observed in Keil et al. 2009) in the risk estimation process for immunotoxicity because it deemed these endpoints to be “insufficiently adverse compared to other endpoints” (p. 245). However, the 2011 IRIS Assessment takes a clear and distinct position on this, stating “[d]ecreased thymus weight reported at relatively low exposures in nonautoimmune-prone mice is a *clear indicator of immunotoxicity* (Keil et al., 2009), and is therefore considered a candidate critical effect” (*emphasis added*).<sup>103</sup> As such, EPA has not provided sufficient justification for dismissing this endpoint from the risk evaluation process and should not do so.

The implications of this decision – in conjunction with the Agency’s dismissal of the Johnson et al. 2003 study as a representative chronic non-cancer study (see Section 4.D. above) – are highly consequential. Utilizing the alternative endpoint of autoimmunity from Keil et al. 2009 results in an approximately 9-fold underestimation of risk compared to what would have been calculated using the Johnson study.

**G. EPA needs to apply an uncertainty factor (UF) to account for lack of dermal toxicity data.**

The draft risk evaluation states (p. 279): “EPA used a previously developed peer-reviewed PBPK model in order to obtain both HECs and HEDs from animal toxicological studies involving either oral or inhalation administration of TCE. The PBPK model does not account for dermal exposure, so EPA relied on traditional route-to-route extrapolation from oral HED values.”

As EDF has commented on for prior draft risk evaluations that have taken a similar approach, EPA’s decision to rely on inhalation-to-dermal extrapolation contributes substantial uncertainty

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<sup>101</sup> EPA IRIS Assessment for Trichloroethylene. 2011. Available at: [https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance\\_nmbr=199#tab-1](https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199#tab-1), p. 5-20.

<sup>102</sup> Ibid.

<sup>103</sup> EPA IRIS Assessment for Trichloroethylene. 2011. Available at: [https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance\\_nmbr=199#tab-1](https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199#tab-1), p. 5-27

to its risk calculations. Therefore, as is recommended for route-to-route extrapolation generally,<sup>104,105</sup> EPA should apply an additional uncertainty factor of 10 to account for these uncertainties.

#### **H. EPA should migrate to a unified approach to presenting dose-specific population risks for both cancer and noncancer endpoints.**

More broadly, EPA must employ health-protective approaches to dose-response modeling, as described at length in the National Academy of Sciences (NAS) report, *Science and Decisions: Advancing Risk Assessment*.<sup>106</sup> Among other recommendations, the NAS argued that “\*\*\*cancer and noncancer responses [to chemical exposures] be assumed to be linear as a default \*\*\*.”<sup>107</sup>

The MOE approach presented in the TCE draft risk evaluation provides a bright-line, yes/no approach to risk and fails to provide a measure of population risk at a given exposure level. This approach limits the assessment’s utility for risk managers, particularly when comparing options for substitution and conducting risk-benefit comparisons.

The National Academy of Sciences (NAS) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA concluded “separation of cancer and noncancer outcomes in dose response analysis is artificial because noncancer endpoints can occur without a threshold or low dose nonlinearity at the population level.”<sup>108</sup> The Committee further stated that background exposures and underlying disease processes can contribute to background risk and lead to linearity at population doses of concern.

This issue was also highlighted in the 2019 NASEM *Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene*:

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<sup>104</sup> 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/>.

<sup>105</sup> Rennen, MA, et al., *Oral-to-inhalation route extrapolation in occupational health risk assessment: a critical assessment*, 39:1 REG. TOXICOLOGY & PHARMACOLOGY 5-11 (2004), <https://www.ncbi.nlm.nih.gov/pubmed/14746775>.

<sup>106</sup> NAT’L RESEARCH COUNCIL, *SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT* (2009), <https://www.ncbi.nlm.nih.gov/books/NBK214630/>.

<sup>107</sup> *Id.* at chp. 5, p. 180.

<sup>108</sup> *Id.* at chp. 5, p. 177.

The committee recommendation, consistent with [NRC \(2009a\)](#), is to include all health end points within a unified framework for dose-response assessment.<sup>109</sup>

EPA should implement the recommendations repeatedly made by the NAS and develop a unified approach to presenting dose-specific population risks for both cancer and noncancer endpoints.

## **5. EPA’s human exposure assessment raises significant questions and concerns.**

### **A. EPA’s unwarranted assumption of respirator and glove use obscures the full extent of unreasonable risk to workers posed by exposure to TCE.**

#### *i. Context and summary*

EPA presents its occupational risk determinations in Section 5.3 (pp. 383-420). While EPA has determined that each condition of use relevant to workers presented an unreasonable risk overall, it still dramatically understates the extent of actual unreasonable inhalation and dermal risks to workers.

As discussed elsewhere in the comments (section 1.B.), EPA has adopted a flawed assumption – absent any empirical evidence to support it – that workers under most industrial/commercial conditions of use of TCE will always wear fully effective personal protective equipment (PPE).

EPA’s application of this assumption to workers under the various conditions of use of TCE dramatically altered its final risk estimates for workers – both in cases where EPA did find a condition of use presented an unreasonable risk overall and in cases where it did not.

In many cases, EPA has used its assumption of PPE to assert that a risk estimate that it found exceeded its risk benchmark in the absence of PPE no longer represents an unreasonable risk. In other cases, EPA found that even with PPE use, a risk estimate still exceeded its benchmark; in those cases EPA presented the risk estimate with PPE as the driver of its determination, thereby understating the magnitude of the actual risk to workers.

To characterize the impact of EPA’s PPE assumption, EDF undertook an analysis of the risk estimates summarized in EPA’s Table 4-54 (pp. 358-369); this table shows: 1) the risk estimates EPA calculated *before* it applied its assumption regarding PPE use; 2) whether EPA’s assumption of PPE could make enough risk go away so that EPA could claim that risk estimate did not represent an unreasonable risk; 3) if so, what degree of PPE efficiency EPA had to assume would be used; and 4) the risk estimates EPA calculated *after* it applied its assumption

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<sup>109</sup> National Academies of Sciences, Engineering, and Medicine. 2019. *Review of DOD’s Approach to Deriving an Occupational Exposure Level for Trichloroethylene*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

regarding PPE use. EDF's analysis is provided in the attached Excel file submitted as Appendix 4 along with these comments.

Our examination revealed the following:

- There are only two kinds of scenarios under which EPA did find that a risk estimate for a given condition of use represented an unreasonable occupational risk:
  - **Scenarios where the risk estimate EPA calculated is so high that it could not make it go away even *after* assuming that workers would always use the most protective PPE that EPA considered.** This would often require use of a highly efficient (and highly cumbersome) respirator with an “assigned protection factor” (APF) of 50, i.e., one that reduces air concentrations by 50-fold, or gloves providing a 10- or 20-fold protection factor (PF).
  - **Scenarios where EPA could not plausibly assume *any* use of respirators.** This applies to EPA's risk determinations for workers under five COUs<sup>110</sup> and for occupational non-users (ONUs) under all conditions of use.
- For nearly all conditions of use where EPA found that its risk estimates for acute, chronic or cancer risks to workers did not represent an unreasonable risk, in order to reach that finding, **EPA had to assume that all of the workers were using respirators or gloves, or both.**
- Even where EPA did find unreasonable risk to workers, **EPA has grossly understated both the extent and magnitude of those risks by assuming use of PPE.**

Put another way: For every one of the conditions of use where EPA could assume PPE might plausibly be used by some workers, EPA either:

- avoided identifying its risk estimates as representing an unreasonable risk *only* by assuming universal, effective use of respirators, gloves, or both; or
- found its risk estimates to represent unreasonable risk even with the use of such respirators or gloves – but, by relying on the risk estimates calculated assuming the PPE, thereby grossly understated both the extent and magnitude of the risk.

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<sup>110</sup> For these five COUs EPA still assumed all workers would wear gloves. The COUs are:

- Industrial/Commercial Use – Cleaning and furniture care products – Carpet cleaner; wipe cleaning
- Industrial/Commercial Use – Laundry and dishwashing products – Spot remover
- Industrial/Commercial Use – Ink, toner, and colorant products – Toner aid
- Industrial/Commercial Use – Apparel and footwear care products – Shoe polish
- Industrial/Commercial Use – Hoof polishes; gun scrubber; pepper spray; other miscellaneous industrial and commercial uses

Consider this example for EPA’s “domestic manufacturing” condition of use, as shown in Table 4-54 (p. 358):

- Absent PPE, all 12 of EPA’s risk estimates for workers exceeded its benchmarks and represented unreasonable risks: 3 endpoints (acute, chronic, and cancer risks) x 2 exposures routes (dermal and inhalation) x 2 exposure levels (high-end and central tendency) = 12 risk estimates; all are boldfaced/shaded in the “no PPE” columns.
- After applying its PPE assumptions:
  - Four of these 12 risk estimates are no longer deemed unreasonable (not boldfaced/shaded).
  - The other eight risk estimates are still unreasonable (boldfaced/shaded) – *but* the magnitude of each of these has been adjusted by a factor representing the level of protection assumed to have been provided by the specified PPE. These adjusted risk estimates are the ones identified by EPA in its final risk determination for this condition of use on p. 383 of the draft risk evaluation.

EPA’s unwarranted approach raises major concerns. First, risk estimates that are not carried over into the final risk determinations may not subsequently be regulated, forgoing EPA’s only opportunity to ensure that PPE it assumed is actually used and workers are protected.

Second and equally or more important in this draft risk evaluation, even though EPA does find all occupational conditions of use do present unreasonable risk to workers, by carrying over into its final risk determinations risk estimates that are understated because of its PPE assumptions, any subsequent regulation EPA promulgates under TSCA will be under-protective of workers.

The magnitude of this underestimation is very large (see subsection ii. below and the “Averages” tab of the Excel file submitted as Appendix 4 along with these comments for details):

- For *acute risks* there is a 16-fold underestimation overall; 50-fold for inhalation exposure, and 14-fold for dermal exposure.
- For *chronic risks* there is a 34-fold underestimation overall; 49-fold for inhalation exposure, and 18-fold for dermal exposure.
- For *cancer risks* there is a 23-fold underestimation overall; 50-fold for inhalation exposure, and 16-fold for dermal exposure.

*ii. Detailed analysis of the effect of EPA’s assumed routine use of PPE on estimates of worker risks*

Based on Table 4-54, EPA estimated worker risks for 102 combinations of industrial/commercial COUs, exposure routes (inhalation or dermal) and exposure levels (high-end or central tendency). For all but seven (i.e., 95) for acute risk as well as five (i.e., 97) for chronic and

cancer risks of these cases, EPA found excessive risk in the absence of PPE. Then in most of these cases, EPA assumed routine use of PPE. Our analysis of these cases found the following:

**ACUTE TOXICITY:** EPA identified excessive risk to workers in 95 cases in the absence of PPE.

- For 44 of the 95 cases, EPA identified no unreasonable risk *only* after assuming the use of PPE.
  - For 23 of those cases EPA assumed use of a respirator:
    - with an APF of 50 for 12 cases; and
    - with an APF of 10 for the other 11 cases.
  - For the other 21 of those cases EPA assumed use of gloves:
    - with a PF of 20 for 3 cases;
    - with a PF of 10 for 17 cases; and
    - with a PF of 5 for 1 case.
- For 5 of the 95 cases, EPA identified unreasonable risk without assuming the use of a respirator.
- For the other 46 of the 95 cases, EPA identified unreasonable risk *even after* assuming the use of PPE (either respirators or gloves).
  - For the 13 cases involving inhalation exposure, even EPA's assumed use of a respirator with an APF of 50 was not enough to eliminate the unreasonable risk.
  - For the other 33 cases involving dermal exposure, even EPA's assumed use of gloves with a PF of 20 (22 cases) or PF of 10 (11 cases) was not enough to eliminate the unreasonable risk.

However, EPA's assumption of PPE use greatly underestimates the magnitude of that unreasonable risk. Averaging the calculated MOEs with and without PPE across these 46 combinations of industrial/commercial COUs, exposure routes (inhalation or dermal) and exposure levels (high-end or central tendency), EPA's PPE assumption yielded MOEs for acute toxicity that were higher than those without PPE:

- by 16-fold overall;
- by 50-fold for inhalation exposure; and
- by 14-fold for dermal exposure.

**CHRONIC TOXICITY:** EPA identified excessive risk to workers in 97 cases in the absence of PPE.

- For 1 of the 97 cases, EPA identified no unreasonable risk *only* after assuming the use of a respirator with an APF of 50.
- For another 6 of the 97 cases, EPA identified unreasonable risk without assuming the use of a respirator.

- For the other 90 of the 97 cases, EPA identified unreasonable risk *even after* assuming the use of PPE (either respirators or gloves).
  - For the 36 cases involving inhalation exposure, even EPA's assumed use of a respirator with an APF of 50 was not enough to eliminate the unreasonable risk.
  - For the 54 cases involving dermal exposure, even EPA's assumed use of gloves with a PF of 20 (42 cases) or PF of 10 (12 cases) was not enough to eliminate the unreasonable risk.

However, EPA's assumption of PPE use greatly underestimates the magnitude of that unreasonable risk. Averaging the calculated MOEs with and without PPE across these 90 combinations of industrial/commercial COUs, exposure routes (inhalation or dermal) and exposure levels (high-end or central tendency), EPA's PPE assumption yielded MOEs for chronic toxicity that were higher than those without PPE:

- by 34-fold overall;
- by 49-fold for inhalation exposure; and
- by 18-fold for dermal exposure.

**CANCER** (Even using EPA's overly lax cancer risk benchmark; see section 7.A.ii.): EPA identified excessive risk to workers in 97 cases in the absence of PPE.

- For 12 of the 97 cases, EPA identified no unreasonable risk *only* after assuming the use of a respirator with an APF of 50 (8 cases) or APF of 10 (4 cases).
- For another 6 of the 97 cases, EPA identified unreasonable risk without assuming the use of a respirator.
- For the other 79 of the 97 cases, EPA identified unreasonable risk *even after* assuming the use of PPE (either respirators or gloves).
  - For the 25 cases involving inhalation exposure, even EPA's assumed use of a respirator with an APF of 50 was not enough to eliminate the unreasonable risk.
  - For the 54 cases involving dermal exposure, even EPA's assumed use of gloves with a PF of 20 (42 cases) or PF of 10 (12 cases) was not enough to eliminate the unreasonable risk.

However, EPA's assumption of PPE use greatly underestimates the magnitude of that unreasonable risk. Averaging the calculated MOEs with and without PPE across these 79 combinations of industrial/commercial COUs, exposure routes (inhalation or dermal) and exposure levels (high-end or central tendency), EPA's PPE assumption yielded cancer risk estimates that were lower than those without PPE:

- by 23-fold overall;
- by 50-fold for inhalation exposure; and
- by 16-fold for dermal exposure.

**B. EPA has underestimated occupational and consumer exposures.**

*i. EPA has failed to consider workers' combined exposure from multiple pathways.*

EPA never considers the combined risks from the inhalation and dermal exposures it calculates – even though many workers could readily experience exposures by both routes, including over the same time period. For example, in the context of estimating dermal exposure, the agency describes TCE's rapid evaporation:

Instantaneous exposures to skin are expected to evaporate before significant dermal absorption occurs based on TCE's physical chemical properties which include the vapor pressure, water solubility and log Kow. (p. 137)

Such rapid evaporation from the skin would lead to increased concentration in the air in the immediate vicinity of the dermally exposed worker. Because both inhalation and dermal exposure result in systemic distribution of TCE, (e.g., EPA states that “[r]egardless of the route of exposure, TCE is widely distributed throughout the body,” p. 203) it is essential to evaluate exposures from both of these routes in combination, including simultaneously, to assess total body burden and the associated effects.

EPA does acknowledge in the draft risk evaluation that workers and consumers may experience both inhalation and dermal exposures simultaneously:

Inhalation and dermal exposures are assumed to occur simultaneously for workers and consumers. (p. 33)

Dermal exposures to liquid TCE are expected to be concurrent with inhalation exposures. (p. 137)

However, EPA quickly dismisses with insufficient justification an additivity approach to assess overall exposure:

EPA chose not to employ simple additivity of exposure pathways at this time within a condition of use because of the uncertainties present in the current exposure estimation procedures, which may may [*sic*] lead to an underestimate or overestimate of the actual total exposure. (pp. 33-34)

EPA's decision not to apply an additivity approach because of "uncertainties" will necessarily result in an underestimate of exposure – something EPA acknowledged in its draft methylene chloride risk evaluation<sup>111</sup> but has failed to do here.

Our concern is reinforced by the comments of several SACC members made during peer review meetings, who called on the agency to combine the inhalation and dermal exposures. The SACC expanded on this concern in several of its reports on earlier draft evaluations. For example:

- 1-Bromopropane SACC Meeting Minutes and Final Report: The SACC stated, "In addition, inclusion of an estimate of combined oral and dermal exposure would be welcome."<sup>112</sup>
- Methylene Chloride SACC Meeting Minutes and Final Report: In responses to Charge Question 6.2 on uncertainties and assumptions not adequately presented, the SACC asked EPA: "Effects of simultaneous dermal and inhalation exposures: Inhalation and dermal exposure to methylene chloride can occur simultaneously. Are effects simply additive (an undiscussed assumption)?"<sup>113</sup>

Another concern raised by a SACC member during the 1,4 dioxane peer review is salient for TCE as well: EPA has ignored all non-occupational baseline exposures workers experience, due to its exclusion of all exposures via environmental releases to air, water, and land. The SACC member argued that the agency at least needs to take these into account as baseline exposures for workers, even if the agency persists in not considering them as arising from conditions of use it has included within the scope of the risk evaluation. In other words, even if the agency does not intend to assess risks from environmental releases of TCE through the air, water, and land (due to its assertions as to the adequacy of actions taken under other statutes), EPA cannot ignore these real-world exposures when assessing the risk TCE presents to an individual.

*ii. EPA may have underestimated exposure to ONUs.*

We support EPA's decision to assume that occupational non-users (ONUs) will not wear respirators. Beyond the concerns we raised earlier with assumptions that workers handling a chemical will consistently wear PPE and that it will be universally effective, it would be even more unrealistic to assume that ONUs would wear any PPE. This point was raised repeatedly by SACC members during their 1,4-dioxane peer review meeting.

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<sup>111</sup> Draft Risk Evaluation for Methylene Chloride, p. 387. Available:

[https://www.epa.gov/sites/production/files/2019-10/documents/1\\_methylene\\_chloride\\_risk\\_evaluation\\_peer\\_review\\_draft\\_heronet\\_public.pdf](https://www.epa.gov/sites/production/files/2019-10/documents/1_methylene_chloride_risk_evaluation_peer_review_draft_heronet_public.pdf).

<sup>112</sup> See here: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061>, p. 13.

<sup>113</sup> See here: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0080>, p. 69.

Nevertheless, EPA may still have underestimated exposure to ONUs in several ways. First, as discussed in detail in section 7.A.iii., EPA assumes central tendency exposures for ONUs in any case where it does not have monitoring data or modeling specific to ONUs.

Second, where EPA does have data to estimate exposure of ONUs specifically, the agency assumes that they are only present in the “far field zone” – i.e., outside of the “near field” workers’ zone (p. 127). However, ONUs may not stay within the “far field zone.” Several SACC members raised this concern during the 1-BP peer review meeting. For example, a SACC member with industrial hygiene experience noted that workers and ONUs may regularly pass into each other’s space, e.g., to communicate or otherwise interact. EPA fails to recognize this. Under section 2.3.1.3 (“Assumptions and Key Sources of Uncertainty for Occupational Exposures”), EPA describes the potential for its method to overestimate exposure to workers – but fails to acknowledge that the converse is true, i.e., the method may underestimate exposure to ONUs.<sup>114</sup>

*iii. EPA has failed to explain or justify its assumption of one exposure event per day.*

In its dermal exposure assessment, EPA assumes one exposure event per day for both workers (pp. 101, 117) and consumers (p. 140). EPA provides little justification for these assumptions.

Yet, for workers, given the typical 8-hour (or longer) work day and the repetition common in many jobs, it seems far more likely that workers would regularly engage in activities that could result in multiple exposure events per day. While EPA recognizes this under its section on assumptions and uncertainties (p. 128), it fails to acknowledge that this assumption will underestimate exposure (as the agency has done for other chemicals, e.g., methylene chloride draft risk evaluation, pp. 165, 375). EPA has not, but must, account for this underestimation and at a minimum provide an uncertainty analysis.

With regards to consumers, EPA also assumes a single exposure event per day, although it does take into account varying durations of exposure (p. 349). This assumption is particularly problematic for “do-it-yourselfers,” which EPA acknowledged may be exposed more than once per day: “EPA assumes that a consumer product would be used only once per day. This is a reasonable assumption for most scenarios, but a Do-It-Yourself- (DIY-) type user could potentially use the same product multiple times in one day” (p. 178). Yet EPA fails to actually address this scenario in calculating exposure and risk estimates.

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<sup>114</sup> “Exposures are calculated by assuming workers spend the entire activity duration in their respective exposure zones (i.e., the worker in the near-field and the occupational non-user in the far-field). Since vapor degreasing and cold cleaning involve automated processes, a worker may actually walk away from the near-field during part of the process and return when it is time to unload the degreaser. As such, assuming the worker is exposed at the near-field concentration for the entire activity duration may overestimate exposure.” P. 127.

EPA also fails to assess any chronic exposures to consumers despite acknowledging in several places in the draft risk evaluation they are expected to occur:

Although high-end frequencies of consumer use are up to 50 times per year, reasonably available toxicological data is based on either single or continuous TCE exposure and it is unknown whether these use patterns are expected to be clustered or intermittent (e.g. one time per week). There is uncertainty regarding the extrapolation from continuous studies in animals to the case of repeated, intermittent human exposures. Therefore, EPA cannot fully rule out that consumers at the high-end frequency of use could possibly be at risk for chronic hazard effects, however it is expected to be unlikely. (p. 136)

[C]hronic exposures were not evaluated for TCE-containing consumer products. However, it is possible that there would be concern for chronic exposure effects for use frequencies greater than intermittent. For example, daily or DIY-type uses of consumer products could constitute a short-term chronic exposure scenario or repeated-acute exposure scenario that is not captured in this evaluation. Identified chronic non-cancer and cancer hazard endpoints (Section 3.2) are unlikely to present for these populations based on reasonably available information, however the possibility cannot be ruled out. For the vast majority of the consumer population which are only exposed through short-term, occasional use of TCE products, only acute exposure is applicable. (p. 178)

While chronic exposure may not be typical for consumers, EPA's failure to assess DIY users as a "potentially exposed or susceptible subpopulation" is troubling. This is especially the case given that EPA implies that it considered DIY users as a sentinel exposure under section 4.4.2:

In terms of this risk evaluation, EPA considered sentinel exposures by considering risks to populations who may have upper bound exposures – for example, workers and ONUs who perform activities with higher exposure potential, or consumers who have higher exposure potential (e.g., *those involved with do-it-yourself projects*) or certain physical factors like body weight or skin surface area exposed. EPA characterized high-end exposures in evaluating exposure using both monitoring data and modeling approaches. (p. 353, emphasis added)

EPA's assumptions about consumer exposure are likely to significantly underestimate the risks they face, which EPA recognizes under section 2.3.2.8.<sup>115</sup> At the very least, EPA needs to

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<sup>115</sup> "However, ease of access to products on-line or in big box stores (like home improvement stores), readily accessible how-to videos, and a consumer movement toward more do-it-yourself

conduct a sensitivity analysis regarding these assumptions in the context of this risk evaluation, which is different than the sensitivity analysis EPA indicates was done on the model itself (p. 516).

*iv. EPA's assessment of dermal exposure likely underestimates exposure due to its crude assumptions about glove use and efficacy.*

As noted above, section 1.B., EPA does not have any actual data on glove use and efficacy, which is necessary to accurately assess dermal exposure. While EPA skirts around this issue in the draft risk evaluation itself, the Supplemental File: Environmental Releases and Occupational Exposure states:

Data about the frequency of effective glove use – that is, the proper use of effective gloves – is very limited in industrial settings. Initial literature review suggests that there is unlikely to be sufficient data to justify a specific probability distribution for effective glove use for a chemical or industry. (p. 223 of supplement)

EPA recognizes the potential for occlusion, whereby glove use can *increase* skin exposure, in both the draft risk evaluation (e.g., “Dermal exposure may be significant in cases of occluded exposure,” p. 116) and the Supplemental File: Environmental Releases and Occupational Exposures (e.g., “Many gloves do not resist the penetration of low molecular weight chemicals... Wearing gloves which are internally contaminated can lead to increased systemic absorption,” p. 221). The agency says that it calculated exposures under occluded scenarios:

EPA also estimated central tendency and high-end dermal retained doses for occluded scenarios for OESs [occupational exposure scenarios] where occlusion was reasonably expected to occur. Occluded scenarios are generally expected where workers come into contact with bulk liquid TCE during use in open systems (e.g., during solvent changeout in vapor degreasing) and not expected in closed-type systems (e.g., during connection/ disconnection of hoses used in loading of bulk containers in manufacturing). (p. 102)

These exposure estimates are reflected in Table 2-15 (p.106); notably, EPA found exposures that are 7.6-12.2 times higher than the no-glove scenarios.<sup>116</sup>

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projects with products containing the chemical of concern could impact the representativeness of the consumer use patterns described within the Westat Survey and may lead to an underestimate of overall consumer exposure.” P. 180.

<sup>116</sup> For most COUs, EPA calculated an occluded exposure of 2,247 mg/day compared to 184.36 mg/day for high end exposure without gloves ( $2,247/184.36 = \mathbf{12.19}$ ). For Commercial Printing

However, it appears that the exposure estimates under occluded conditions are not actually incorporated at all into the ultimate risk estimates and risk determinations for the occupational scenarios. For example, when one compares Table 2-15 to Tables 4-6 through 4-27, the occluded exposure scenarios appear to disappear from the risk estimates shown in the latter tables. Likewise, occluded scenarios do not appear in the Supplemental Information File: Risk Calculator for Occupational Exposures (e.g., see tab “RR” in EPA’s “TCE-Risk Calculator for Occupational Exposures” spreadsheet).<sup>117</sup> If EPA did in fact incorporate occlusion into its ultimate risk estimates and risk determinations, it needs to be far clearer on how it did so.

Instead, the agency simply uses default glove protection factors, ignoring the elevated dermal exposures of workers in occluded scenarios. More specifically, the agency assumes fixed protection factors (PFs) of 5x, 10x, and 20x. While EPA has now described somewhat more detailed scenarios for each assumed PF (see Table 2-20, p. 117), they do not appear to be supported by any empirical data that account for the complexities of glove use in the real world. EPA skirts around the issue in this draft risk evaluation, but previously acknowledged in the draft methylene chloride risk evaluation that the glove protection factors are ““what-if” assumptions and are uncertain” (methylene chloride draft risk evaluation, p. 166).<sup>118</sup> Further, the agency fails to acknowledge the uncertainties and deficiencies in its glove use assumptions in the Risk Determination section of this draft risk evaluation.

During both the 1,4-dioxane and 1-BP SAAC peer review meetings, a SACC member who is a dermal exposure expert expressed his concern with EPA’s approach, which EPA has repeated for each chemical, including TCE. He noted that glove testing is typically conducted in a lab under ideal conditions – without an actual human hand present. However, in the real world, an insufficiently trained or attentive user may contaminate a glove, leading to occlusion and higher exposure. Likewise, permeable gloves may enable the chemical to be absorbed through the glove, while preventing or slowing evaporation. Gloves can also increase skin temperature and humidity, which can increase absorption. Therefore, the assumption that PFs can only range as low as 1x (no gloves) is erroneous; rather, the range should include PFs below 1x.

With regard to consumers, while EPA considered scenarios with impeded evaporation (e.g., rag soaked with TCE), it appears that EPA did not assume any use of gloves. While it is a reasonable assumption that many consumers would not seek out, purchase, and wear gloves capable of protecting the user from TCE, it is also reasonable to assume that some consumers

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and Copying, EPA calculated an occluded exposure of 786 mg/day compared to 101.3 mg/day for high end exposure without gloves (786/101.3 = **7.59**).

<sup>117</sup> TCE-Risk Calculator for Occupational Exposures, Excel spreadsheet, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0500-0021>.

<sup>118</sup> Available here: [https://www.epa.gov/sites/production/files/2019-10/documents/1\\_methylene\\_chloride\\_risk\\_evaluation\\_peer\\_review\\_draft\\_heronet\\_public.pdf](https://www.epa.gov/sites/production/files/2019-10/documents/1_methylene_chloride_risk_evaluation_peer_review_draft_heronet_public.pdf).

may well use insufficiently protective gloves that allow TCE to permeate through the material, such as simple latex gloves that are readily found in home improvement stores that sell TCE-containing consumer products. But EPA fails to consider improper glove use and its potential to lead to occlusion and, thus, potentially higher exposure than the no-gloves/soaked rag assumption on which EPA relies (e.g., greater surface area exposed, longer duration of exposure). While EPA argues that it may have overestimated consumer dermal exposure from use of a soaked rag (p. 178), EPA's assumptions for soaked rags likely do not overestimate the exposure duration or surface area exposed when occlusion occurs during a consumer's use of gloves.

With regard to workers, 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 – regardless of the potential for occlusion in the workplace – without citing any evidence to support these values. As described in section 5.A.ii., in 21 cases EPA found that central-tendency dermal exposures did not present unreasonable acute risks only by assuming workers in those scenarios always wore gloves that consistently provided the assumed PF. In these cases, the unstated, but highly questionable, premise seems to be that if gloves potentially available can be assumed to provide a PF that reduces risk to below the benchmark, then EPA can conclude there is no unreasonable risk. This approach will allow clear risks to occur whenever a worker uses anything less than the assumed gloves (or no gloves), or when there is occlusion; these scenarios are quite likely – and certainly reasonably foreseen – to occur in the real world.

*v. EPA may underestimate dermal exposure based on absorption assumptions*

EPA assumed a dermal absorption rate of 8% in industrial settings and 13% in commercial settings based on the Kasting and Miller, 2006 model and the following assumptions:

The steady state fractional absorption (fabs) for TCE is estimated to be 0.08 in industrial facilities with higher indoor wind flows or 0.13 in commercial facilities with lower indoor wind speeds based on a theoretical framework provided by Kasting and Miller (2006) (Kasting and Miller, 2006), meaning approximately 8 or 13 percent of the applied dose is absorbed through the skin following exposure, from industrial and commercial settings, respectively. (p. 117)

However, elsewhere EPA indicates that dermal absorption is rapid:

Rapid absorption through the skin has been shown by both vapor and liquid TCE contact with the skin. In several human volunteer studies, both TCE liquid and vapors were shown to be well absorbed in humans via the dermal route. Dermal absorption was rapid following exposures of between 20 and 30 minutes, with

peak TCE levels in expired air occurring within 15 minutes (liquid) and 30 minutes (vapor) (U.S. EPA, 2011e). Dermal exposure to TCE disrupts the stratum corneum, impacting the barrier function of skin and promoting its own absorption. Therefore, absorption may increase at a greater than linear rate due to increasing epidermal disruption over time (ATSDR, 2019). (p. 203)

It is unclear whether EPA considered this latter research when setting the fractional absorption rates of 8% and 13%. If not, the Kasting and Miller, 2006 model may underestimate dermal exposure from TCE, given the cited human and excised skin tissue studies specific to TCE.

### **C. EPA's workplace exposure monitoring data present several concerns.**

- i. EPA inappropriately relies solely on occupational exposure data from the Halogenated Solvents Industry Alliance for three conditions of use.*

For the “Manufacturing,” “Processing as a Reactant,” and “Other Industrial Uses” conditions of use (COU), EPA relies solely on data voluntarily submitted by the Halogenated Solvents Industry Alliance (HSIA) to the agency in 2018 (collected in 2016).<sup>119</sup> For the latter two COUs, EPA uses HSIA's manufacturing data as surrogate monitoring data.

HSIA is the main trade association for manufacturers of TCE, and, as such, it has a strong vested interest in EPA finding the chemical present as low a risk as possible. This vested interest calls into question the reliability and completeness of the data voluntarily submitted by HSIA. We have previously commented extensively on the shortcomings of EPA's reliance on data voluntarily submitted by industry; see, for example, our comments to the agency on the draft methylene chloride risk evaluation; we incorporate those comments by reference.<sup>120</sup>

In its systematic review process, EPA rated the HSIA data as 1.6, or “High.”<sup>121</sup> In doing so, EPA made some questionable decisions. First, EPA assigned the data a score of “1” for Geographic Scope because the data come from U.S. facilities. However, the data represent only

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<sup>119</sup> Halogenated Solvents Industry Alliance Problem Formulation Comments on TCE (Aug. 2018), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0103>.

<sup>120</sup> See EDF Comments on Draft Risk Evaluation of Methylene Chloride, pp. 147-149. December 30, 2019. Available at: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0042>.

<sup>121</sup> This rating applies to the HSIA data dated 2018, the review of which appears on p. 228 of Systematic Review Supplemental File: Data Quality Evaluation of Environmental Release and Occupational Exposure Data, at [https://www.epa.gov/sites/production/files/2020-02/documents/6\\_tce-data\\_quality\\_evaluation\\_of\\_environmental\\_releases\\_and\\_occupational\\_exposure\\_data.pdf](https://www.epa.gov/sites/production/files/2020-02/documents/6_tce-data_quality_evaluation_of_environmental_releases_and_occupational_exposure_data.pdf).

one manufacturing facility (“Company B,” see p. 698); it is highly unlikely that workplace monitoring data from a single manufacturing site are representative of the entire country.<sup>122</sup>

Second, EPA scored the HSIA data a “1” for “Sample Size,” even though the dataset is only comprised of a mere 16 samples.

Third, as EPA acknowledges, HSIA has not provided a standard description of the methods used to collect the data or to analyze the samples. EPA assigned the 2018 data a “3” for Methodology explaining that “no method provided by the HSIA Industry organization.” However, EPA’s approach to weighting criteria, which is inconsistent with best practices in systematic reviews, results in the “Low” Methodology score having little impact on the overall score.

Fourth, and more broadly, EPA’s systematic review protocol does not take into consideration the potential for bias based on the data source. EPA provides insufficient justification for its exclusive reliance upon this potentially biased data without independent validation and quality assurance reporting. Shockingly, EPA raises potential bias concerns with OSHA data (see subsection ii. below), while failing to acknowledge the significant potential bias in the HSIA data.

While there may be a role for the data submitted by HSIA in the risk evaluation, it is inappropriate for EPA to rely solely on these data for several COUs. EPA has not adequately compared HSIA’s data to that available through OSHA; see further discussion below.

*ii. EPA appears to have ignored OSHA data and dismisses it as “biased”*

OSHA has collected a significant amount of data on TCE exposure since the mid-1980s. Our own search using the OSHA Chemical Exposure Health Data tool<sup>123</sup> yielded 3,225 air samples for TCE dated as recently as December 2018. However, it appears that EPA only relied on OSHA data for a single condition of use (Metalworking Fluids, 3 data points) and incorporated

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<sup>122</sup> EPA’s 2016 Chemical Data Reporting data (*see* 2016 CHEMICAL DATA REPORTING RESULTS, <https://www.epa.gov/chemical-data-reporting/2016-chemical-data-reporting-results> (last visited March 11, 2020)) identified by name and location three U.S. facilities manufacturing TCE, but also listed records for two additional facilities for which the submitter had claimed as confidential business information (CBI) whether the facility produced or imported methylene chloride. In addition, EPA has withheld that information for one additional facility. Moreover, there may be additional facilities that did not report, given that only companies that manufacture or imported 25,000 pounds or more at a site during the reporting period were required to report information under the CDR rule. So it is not possible to discern from these data how many more than three facilities manufacture TCE in the U.S.

<sup>123</sup> CHEMICAL EXPOSURE HEALTH DATA, <https://www.osha.gov/opengov/healthsamples.html> (last visited March 11, 2020).

OSHA data into an additional two conditions of use (Adhesives, Sealants, Paints, and Coatings as well as Spot Cleaning and Wipe Cleaning, <8 data points). It is unclear why the other OSHA data – which are not even mentioned in the systematic review supplemental file on environmental releases and occupational exposure<sup>124</sup> – have not been incorporated.

OSHA similarly has collected significant data on methylene chloride; for that chemical, Dr. Adam Finkel, a former OSHA official, submitted public comments to the agency in 2017 including the OSHA dataset from 1984-2016.<sup>125</sup> While EPA did not utilize those data to their full extent,<sup>126</sup> the agency did incorporate them to a significant extent into its draft methylene chloride risk evaluation. In contrast, here it appears that EPA has simply ignored the bulk of the OSHA data.

In finalizing the risk evaluation, EPA must acquire all of the relevant OSHA data on TCE in order to comply with its requirements to consider reasonably available information and the best available science, in accordance with TSCA section 26.

Furthermore, EPA inappropriately singles out OSHA data as potentially biased in the draft TCE risk evaluation:

Some data sources may be inherently biased. For example, bias may be present if exposure monitoring was conducted to address concerns regarding adverse human health effects reported following exposures during use. Similarly, OSHA CEHD are obtained from OSHA inspections, which may be the result of worker complaints, and may provide exposure results that may generally exceed the industry average. (p. 126)

EPA's decision to highlight potential bias in OSHA data – while neglecting to mention potential bias in the industry data on which it relies – is unjustified and likely inaccurate. For example, Dr. Finkel debunked this argument in 2017 comments he submitted to the agency:

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<sup>124</sup> Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data. Available at: [https://www.epa.gov/sites/production/files/2020-02/documents/6\\_tce-](https://www.epa.gov/sites/production/files/2020-02/documents/6_tce-data_quality_evaluation_of_environmental_releases_and_occupational_exposure_data.pdf)

[data\\_quality\\_evaluation\\_of\\_environmental\\_releases\\_and\\_occupational\\_exposure\\_data.pdf](https://www.epa.gov/sites/production/files/2020-02/documents/6_tce-data_quality_evaluation_of_environmental_releases_and_occupational_exposure_data.pdf).

<sup>125</sup> Comment by Dr. Adam M. Finkel on Regulation of Certain Uses under Toxic Substances Control Act: Methylene Chloride and N-Methylpyrrolidone at 3 (May 19, 2017), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0231-0536>.

<sup>126</sup> See EDF Comments on Draft Risk Evaluation of Methylene Chloride, pp. 53-55. December 30, 2019. Available at: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0042>.

As an industrial hygienist and former OSHA Regional Administrator, I find the notion that OSHA air sampling data are biased upwards to be facile. OSHA receives very few employee complaints about health issues (as opposed to safety hazards), and inspections within the sectors it targets for inspection are (by law) random, not aimed at likely violators. Counteracting the tendency (if it exists) for OSHA to gravitate towards less-compliant facilities is the strong downward bias inherent in the fact that OSHA does not tend to inspect very small (10 or fewer employees) establishments in proportion to their abundance in the economy; these facilities tend to have higher chemical exposures, and they are especially abundant in the paint/coating SICs.<sup>127</sup>

*iii. There are apparent errors in EPA's characterization of exposure monitoring systematic review rankings.*

EPA appears to have mischaracterized its own systematic review data quality rankings in the draft risk evaluation for several exposure monitoring data sources. While we have not checked each instance, we have identified and raise here the following errors in Table 2-26:

- **Batch Open-Top Vapor Degreasing**
  - EPA states on p. 129: “These monitoring data include 123 data points from 16 sources, and the data quality ratings from systematic review for these data were *medium*.” (emphasis added)
  - Based on the description on p. 705, the referenced data sources appear to be from these 10 studies: Daniels et al., 1988, Ruhe et al., 1981, Barsan, 1991, Ruhe, 1982, Rosensteel and Lucas, 1975, Seitz and Driscoll, 1989, Gorman et al., 1984, Gilles et al., 1977, Vandervort and Polakoff, 1973, and Lewis, 1980.
  - In the document “Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data,” all 10 studies received an overall quality determination of *high*, not medium.
  
- **Spot Cleaning and Wipe Cleaning**
  - EPA states on p. 133: “These monitoring data include 8 data points from 2 sources, and the data quality ratings from systematic review for these data were *medium*.” (emphasis added)
  - Based on the description on p. 732, the referenced data sources appear to be Burton and Monesterskey, 1996 and NIOSH, 1997.

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<sup>127</sup> Comment by Dr. Adam M. Finkel on Regulation of Certain Uses under Toxic Substances Control Act: Methylene Chloride and N-Methylpyrrolidone at 4 (May 19, 2017), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0231-0536>.

- In the document “Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data,” both Burton and Monesterskey, 1996 and NIOSH, 1997 received an overall quality determination of *high* (1.6 and 1.4, respectively; see p. 159 and 172 of the systematic review supplemental file), not medium.
- **Commercial Printing and Copying:**
  - EPA states on p. 134: “These monitoring data include **20** data points from 1 source, and the data quality ratings from systematic review for these data were *medium*.” (emphasis added)
  - Based on the description on p. 737, the referenced data source appears to be Finely and Page, 2005.
  - In the document, “Systematic Review Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data,” Finely and Page, 2005 received an overall quality determination of *high* (1.6) and had 23 samples (see p. 126 of the systematic review supplemental file), not medium.

These apparent errors call into question EPA’s ultimate “overall confidence” ratings for the inhalation exposure estimates presented in Table 2-26 (pp. 128-134).

#### **D. EPA’s “PEL-capped” analysis is inappropriate.**

In the draft risk evaluation, EPA conducted a “PEL-capped” analysis, whereby the agency calculated exposure estimates only using data points below the OSHA PEL of 100 ppm. EPA found:

a reduction of the high-end acute exposure estimate from 25.92ppm [*sic*] to 19.23 ppm and the central tendency acute exposure estimate from 4.60 ppm to 4.26 ppm. Chronic high-end and central tendency exposures are reduced from 17.75 ppm and 3.15 ppm to 13.17 ppm and 2.92 ppm, respectively. Lifetime exposures are reduced from 9.10 ppm and 1.25 ppm to 6.75 ppm and 1.15 ppm, respectively. The reduced exposures do not significantly affect the risk estimates, since exposures were only reduced by up to ~30%. (p. 288)

It appears that EPA ultimately did not incorporate this analysis into the final risk estimates because “MOEs remains orders of magnitude below the benchmark MOE” (p. 288). The implication is that if EPA were to have found that the PEL-capped analysis impacted the risk determinations, it may have relied upon this approach.

Presumably EPA pursued this analysis under an assumption of compliance with OSHA’s PEL standard. EPA’s approach is flawed. First, EPA must utilize the full dataset, regardless of

whether data points are above or below the PEL. Second, if anything, the data indicate exactly the opposite of what EPA assumes: the existence of real-world exposure monitoring data above the PEL demonstrate that non-compliance is both known to occur and is reasonably foreseeable. It is inappropriate for EPA to consider excluding data points collected in the real world on the basis of its flawed assumption of universal compliance with regulatory requirements.

**E. EPA did not rely on either an aggregate or sentinel exposure assessment.**

“In conducting a risk evaluation \*\*\*, [EPA] shall—describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration.” 15 U.S.C. § 2605(b)(4)(F)(ii). As explained below, EPA did not prepare aggregate exposure assessments, and it did not establish that it prepared adequate sentinel exposure assessments, in its risk evaluation. EPA has failed to explain how its decision to rely on other exposure assessments can be reconciled with TSCA § 6(b)(4)(F)(ii).

*i. EPA did not perform an aggregate exposure assessment.*

EPA’s regulations define “[a]ggregate exposure [as] the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways.” 40 C.F.R. § 702.33. In the draft risk evaluation, EPA did not actually prepare an aggregate exposure assessment. (pp. 352-353). EPA states that:

aggregating dermal and inhalation exposure for risk characterization was not appropriate due to uncertainties in quantifying the relative contribution of dermal vs inhalation exposure, since dermally applied dose could evaporate and then be inhaled. Aggregating exposures from multiple routes could therefore inappropriately overestimate total exposure, as simply adding exposures from different routes without an available PBPK model for those routes would compound uncertainties. (pp. 352-353)

However, EPA’s statement does not explain why a worker’s inhalation of part of a dermally applied dose would lead to an overestimate of the total dose experienced by the individual, or could not be accounted for in an aggregate exposure assessment. Notably, EPA does not dispute that failing to aggregate inhalation and dermal exposures may lead to an underestimate of exposure as it ignores the reality that exposure from dermal and inhalation routes would be combined. Thus, EPA underestimates exposure. EPA then invokes uncertainty as its excuse for that underestimation. To the extent there are uncertainties in an aggregating analysis, such uncertainties do not support assuming exposure is less than the sum of the exposures; by not combining the exposures it is far more likely that EPA is underestimating the exposure than overestimating it. Uncertainty does not justify ignoring the fact that these exposures are actually experienced in combination.

Notably, EPA did not merely fail to combine exposures between inhalation and dermal exposure pathways; EPA also failed to combine any exposures from multiple conditions of use. Instead, EPA looked at each condition of use separately: “EPA also did not consider aggregate exposure among individuals who may be exposed both in an occupational and consumer context because there is insufficient information reasonably available as to the likelihood of this scenario or the relative distribution of exposures from each pathway.” (p. 353). EPA could have used its information authorities to gain more information about these scenarios, and in any event, it is reasonably foreseeable that a person who uses TCE in an occupational context would also use it as a consumer. It is also reasonably foreseeable that a worker or consumer might use or otherwise be exposed to TCE in more than one use over time; EPA did not address the potential for multiple exposures to the same individual worker or consumer. Thus, EPA failed to assess “the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways.” 40 C.F.R. § 702.33.

To accurately assess overall exposure to TCE, EPA should prepare an exposure assessment that actually looks at “the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways.” 40 C.F.R. § 702.33. Such an exposure assessment should combine exposures from both the inhalation and dermal pathways, and EPA should also consider the scenarios where individuals are exposed via multiple conditions of use.

EPA has not justified its decision to forego an aggregate exposure assessment beyond invoking “uncertainty,” which is not a justification for underestimating the overall exposure to TCE.

- ii. EPA did not establish that its so-called sentinel exposure assessments actually reflect “the plausible upper bound of exposure,” as required by EPA’s regulation, and EPA did not rely on sentinel assessments in its risk characterizations.*

EPA’s regulations describe “[s]entinel exposure [as] the exposure from 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.” 40 C.F.R. § 702.33. In the draft risk evaluation, EPA stated:

In terms of this risk evaluation, EPA considered sentinel exposures by considering risks to populations who may have upper bound exposures – for example, workers and ONUs who perform activities with higher exposure potential, or consumers who have higher exposure potential (e.g., those involved with do-it-yourself projects) or certain physical factors like body weight or skin surface area exposed. EPA characterized high-end exposures in evaluating exposure using both monitoring data and modeling approaches. Where statistical data are reasonably available, EPA typically uses the 95th percentile value of the reasonably available dataset to characterize high-end exposure for a given condition of use. For

consumer and bystander exposures, EPA characterized sentinel exposure through a “high-intensity use” category based on both product and user-specific factors.

(p. 353). However, EPA did not establish that the exposures it analyzed represent the “plausible upper bound of exposure relative to all other exposures” within the relevant categories. This regulatory definition requires that, when EPA prepares a sentinel exposure assessment for workers or consumers, EPA must identify or evaluate the worker or consumer whose exposure represents the upper bound of exposure. 82 Fed. Reg. 33,726, 33,733 (July 20, 2017). EPA has not established that, for each category of exposure, it actually identified and evaluated the worker or consumer whose exposure represents the plausible upper bound of exposure.

Perhaps most importantly, EPA has not stated whether, in identifying sentinel exposures for workers, EPA assumed use of personal protective equipment (PPE). To accurately assess “the plausible upper bound of exposure,” EPA should consider exposures without any PPE unless EPA can establish that PPE is *always and effectively* used for the particular condition of use. As discussed in section 1.B., EPA does not have data sufficient to establish this.

Notably, it is clear that in making its risk determinations, EPA assumed PPE use. *Compare* p. 383 (using values with PPE assumption), *with* p.358 (Chart providing values for both no PPE and with assumption of PPE). See also section 5.A. of these comments. Therefore, as a practical matter, EPA did not rely on sentinel exposures—the “plausible upper bound of exposure relative to all other exposures”—in developing its risk characterizations.

\* \* \* \* \*

Thus, EPA’s risk characterizations did not rely on either aggregate or sentinel exposure assessments. EPA has not explained how its approach is consistent with TSCA § 6(b)(4)(F)(ii). To accurately assess the total risk presented by TCE, EPA needs to consider combined exposures, including those faced by the most exposed individuals. In EDF’s view, EPA should prepare an actual aggregate exposure assessment.

## **6. EPA’s environmental assessment raises a number of questions and concerns.**

### **A. EPA’s approach and methodology for assessing environmental exposure ignore or over-simplify fate characteristics and ignore key data.**

In its problem formulation for TCE, EPA states:

TCE is widely detected in a number of environmental media. While the primary fate of TCE released to surface waters or surface soils is volatilization, TCE is more persistent in

air and ground water, where it is commonly detected through national and state-level monitoring efforts. TCE is *frequently* found at Superfund sites as a contaminant in *soil* and ground water. (p. 33, emphasis added)

Despite acknowledging TCE's documented persistence in environmental media other than surface water, EPA dismisses these potential impacts outright, simply because they are not the "primary fate" of TCE. By considering only water releases, EPA ignored the 48,245 pounds of TCE released on-site for land disposal.<sup>128</sup> Updated TRI data from 2018 show "other" TCE releases to land totaled nearly 157,000 pounds.<sup>129</sup> This release appears to be from a single facility that seems to have been discharging TCE to land for a number of years.<sup>130</sup> It is unclear how this facility is permitted for such a discharge.

EPA has given TRI and DMR data a "medium" confidence rating due to potential underreporting because of limitations to the reporting requirements under these programs (p. 77). Hence, the data cited above likely understate the extent of discharges of TCE to the environment.

EPA itself has previously highlighted the environmental concern from TSCA-uses of TCE, stating in its 2014 work plan risk assessment:

The absence of an environmental risk assessment of the TCE TSCA uses should not be construed as saying that the fate and transport properties of TCE suggest that water and soil contamination is likely low or do not pose an environmental concern.\*\*\* While the primary concern with this contamination has been human health, there is potential for TCE exposures to ecological receptors in some cases.<sup>131</sup>

TCE is a well-studied chemical with a long history of documented environmental impact. For EPA now to dismiss environmental impacts to soil and sediment based on predicted

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<sup>128</sup> See p. 32 of Problem Formulation.

<sup>129</sup> US EPA. (2020). TRI Explorer (2018 National Analysis Dataset, released November 12, 2019). Retrieved from <https://enviro.epa.gov/triexplorer/>. Accessed March 12, 2020; "Other land disposal" defined as: Other land disposal is the disposal of the toxic chemical to land at the facility that does not fall into one of the other on-site land release categories found in Sections 5.5.1 through 5.5.3 on the TRI Form R. Other disposal includes such activities as placement in waste piles and spills or leaks. Data from Section 5.5.4 on the TRI Form R.

<sup>130</sup> *Id.* See Other Land Disposal (On-Site) for the US DOE Waste Isolation Pilot Plant in Carlsbad, NM; see also USEPA ECHO Detailed Facility Report (2020) <https://echo.epa.gov/detailed-facility-report?fid=110060818735#overEnvirofactsReport>

<sup>131</sup> US EPA (2014). TSCA work plan chemical risk assessment. Trichloroethylene: Degreasing, spot cleaning and arts & crafts uses. (740-R1-4002). Washington, DC: Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. P. 30.

environmental partitioning does not represent consideration of the best available science or reasonably available information.

*i. Partitioning coefficients do not account for an inherently non-equilibrated system.*

Physical-chemical properties of a chemical can describe its ultimate environmental fate characteristics. EPA used measured properties and EPISuite to predict a number of important environmental fate characteristics based on those properties, which it then coupled with assumptions about particular conditions of use to justify disregarding pathways of exposure to sediment and terrestrial organisms.

Importantly, partition coefficients assume chemical equilibrium has been established. However, chemicals of concern can occur in high concentrations in different environmental compartments prior to reaching equilibrium. When considering an open, multi-media system, a better approach for approximation might be the Level III Fugacity model, which predicts that 9.9% of TCE will be distributed to soil, 36.8% to air, 53% to water, and the remainder (0.26%) to sediment, as calculated using EPISuite 4.11. A 10% percent distribution to soil cannot be dismissed as *de minimis*.

Outlined below are examples of how using estimated or even measured partition coefficients to calculate residence in soil, soil-vapor, and water may lead to erroneous conclusions.

*a. Reliance on physical-chemical parameters can lead to underestimation of TCE partitioned to soil.*

EPA reported that the organic carbon:water partition coefficient (Log  $K_{OC}$ ) for TCE ranged between 1.8 and 2.17, which generally suggests that soil and sediment sorption of TCE is low. Other EPA sources cite a moderately higher Log  $K_{OC}$  of 2.4, and note that in practice, "[m]easured partition coefficients, however, *may be considerably higher than calculated values*, especially at lower aqueous concentrations.<sup>132</sup> Hence the predicted value EPA relies on for TCE associated with soil could well *underestimate* what is actually present.

*b. The high volatility of TCE leads to air exposure through releases to soil and water, not just through direct emissions to ambient air.*

EPA acknowledges that TCE is expected to volatilize to air, based on physical-chemical properties (p. 275) and the STP model in EPISuite, which predicted 80% removal via volatilization (p. 70). When TCE moves to the atmosphere, it's half-life through degradation by

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<sup>132</sup> US EPA (1992). TCE Removal from Contaminated Soil and Ground Water. (EPA/540/S-92/002). Washington, DC: Office of Solid Waste and Emergency Response.

reactants in the atmosphere is nearly two weeks,<sup>133</sup> which has led EPA to conclude that "long range transport is possible" (See Problem Formulation, p. 30). The logical conclusion is that land-applied TCE and TCE-contaminated wastewater sent to treatment facilities are likely an important source of air-exposures of TCE, which EPA has not addressed.

Furthermore, it is important to note that this type of degradation will only occur in the atmosphere. However, migration of TCE in soil does not always result in volatilization to the atmosphere. EPA notes that, "[o]nce in soil, TCE can become associated with soil pore water, enter the gas phase because of its Henry's Law constant, or exist as a nonaqueous phase liquid (NAPL). It is possible that upward or downward movement of TCE can occur in each of these three phases\*\*\*." <sup>134</sup>

TCE present in soil vapor (a well-documented phenomenon primarily recognized through soil vapor intrusion into indoor air<sup>135</sup>) will not degrade via atmospheric reactions. EPA has disregarded impacts from such exposure to terrestrial organisms whose habitat exists in the vadose zone. Fossorial and semi-fossorial organisms (those that burrow) or have an "increased exposure potential from inhalation at site contaminated with volatile chemicals in the subsurface." <sup>136</sup> EPA has ignored these sources of environmental exposure to such organisms.

*c. The physical-chemical properties of TCE will lead to longer half-lives in water than predicted by the EPISuite volatilization module, which likely biases predictions of concentrations in surface water to be artificially low.*

In its draft risk evaluation, EPA reports the modeled volatilization half-life of TCE in a model river will be 1.2 hours and the half-life in a model lake will be 110 hours (p. 259). Importantly, TCE is a dense non-aqueous phase liquid (DNAPL). In its 2014 TCE work plan risk assessment, EPA notes that:

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<sup>133</sup> TCE has an estimated atmospheric half-life of about 13 days (using Version 4.10 of EpiSuite, EPA, 2012b).

<sup>134</sup> US EPA (2014). TSCA work plan chemical risk assessment. Trichloroethylene: Degreasing, spot cleaning and arts & crafts uses. (740-R1-4002). Washington, DC: Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. Pp. 158-159.

<sup>135</sup> See: <https://www.epa.gov/vaporintrusion/vapor-intrusion-superfund-sites#tri>

<sup>136</sup> Gallegos P, Lutz J, Markwiese J, Ryti R, Mirenda R. 2007. Wildlife ecological screening levels for inhalation of volatile organic chemicals. *Environmental Toxicology and Chemistry*. 26(6):1299–1303. doi:[10.1897/06-233R.1](https://doi.org/10.1897/06-233R.1).

Volatilization from water surfaces will be an important fate process based upon TCE's measured Henry's Law constant. However, its density may cause it to sink in the water column, potentially *increasing the aquatic residence time of TCE*.<sup>137</sup>

The TCE work plan risk assessment further notes that the "[v]olatilization half-lives in an experimental *field* mesocosm consisting of seawater, planktonic, and microbial communities ranged from 10.7 to 28 days," contrasting those values to values measured "half-lives of evaporation from *laboratory* water surfaces (distilled water) [that] have been reported to be on the order of several minutes to hours, depending upon the turbulence." This suggests that the volatilization half-life used by EPA in this evaluation is too low. Even considering less-turbulent water bodies (lakes), the half-life reported by EPA is one-half to one-fifth the value of that found in natural conditions.

The density of TCE, coupled with its relatively low solubility, indicates that sampling surface water using grab samples at the tops of water columns will bias the analysis, resulting in artificially low environmental concentrations. Hence, such an approach to sampling may not represent the actual concentrations of TCE found in surface water.

*ii. EPA has ignored STORET data available for evaluating sediment impacts.*

Importantly, sampling only surface water overlooks a potentially more likely environmental compartment for a chemical that is denser than water. As a DNAPL, TCE is likely to be present in the sediment, at the bottom of a water column.

In its problem formulation EPA noted that the STORET database would be examined for recent data on TCE levels in sediment (p. 34). However, these data are absent from the draft risk evaluation. Instead EPA states that it "included a *qualitative* assessment describing trichloroethylene exposure from sediments for aquatic organisms" because TCE "is not expected to accumulate in sediments" (p. 31, emphasis added).

We reviewed data reported in the National Water Quality Monitoring Council database of Water Quality Data<sup>138</sup> for TCE in sediment (above detection) in the last 10 years. We applied the same qualifiers for sediment that EPA used for surface water (as described in section 2.2.4.2 of the

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<sup>137</sup> US EPA (2014). TSCA work plan chemical risk assessment. Trichloroethylene: Degreasing, spot cleaning and arts & crafts uses. (740-R1-4002). Washington, DC: Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. P. 157 (emphasis added).

<sup>138</sup>See:

[https://enviro.epa.gov/triexplorer/release\\_fac?p\\_view=USFA&trilib=TRIQ1&sort=RE\\_TOLBY&sort\\_fmt=2&state=All+states&county=All+counties&chemical=000079016&industry=ALL&year=2018&tab\\_rpt=1&fld=RELLBY&fld=TSFDSP&OTHDISPD=Y](https://enviro.epa.gov/triexplorer/release_fac?p_view=USFA&trilib=TRIQ1&sort=RE_TOLBY&sort_fmt=2&state=All+states&county=All+counties&chemical=000079016&industry=ALL&year=2018&tab_rpt=1&fld=RELLBY&fld=TSFDSP&OTHDISPD=Y) (last accessed March 13, 2020).

draft risk evaluation); we did not exclude sites with "known contamination," nor did we include samples below detection. This analysis resulted 21 quantifiable analyses of TCE in sediment; the maximum detected concentration was 26,000 ug/kg.

EPA overlooked these data, which are environmentally relevant and describe measured impacts to environmental systems simply because of its assertion that TCE "is not expected to accumulate in sediments" (p. 31).

*iii. EPA has overlooked important considerations for the anaerobic biodegradation of TCE.*

EPA has concluded, based on its review of test data that the rate of anaerobic biodegradation is "fast" (p. 70). We do not disagree that under ideal conditions with correct microbial consortia that carry the metabolic capability to reductively dehalogenate TCE to ethene,<sup>139</sup> this conclusion is valid; however, there are important caveats to this conclusion this conclusion is valid; however, there are important caveats to this conclusion that must be considered. EPA goes on to acknowledge that there is inherent variability in the reported biodegradation rates that arises from "methodology, interlaboratory variability and variability due to factors such as the specific microbial populations used, water, soil and sediment chemistry, oxygen concentration/redox potential, of the collected samples used in the study, temperature and test substance concentration." Yet EPA still concludes that the "weight of evidence shows \*\*\* the anaerobic biodegradation in anaerobic condition is fast" (p.71).

Biologically mediated processes that transform compounds cannot be assumed to lead to complete removal of a compound. Notably, under anaerobic conditions, TCE biologically degrades via sequential removal of chloride ions first to cis-dichloroethene, and next to vinyl chloride, which is itself a potent carcinogen. Vinyl chloride degradation to ethane (under anaerobic conditions) is often the rate-limiting step in this transformation, as it is mediated by a select group of microorganisms. As the rate-limiting step, there are many documented cases of stalled TCE-degradation, which has led to elevated vinyl chloride concentrations in the environment<sup>140</sup> – arguably a condition as bad as or worse than TCE alone.

Where TCE is discharged into the environment, simply reporting standard biodegradation rates can obscure important impacts due to transformation processes.

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<sup>139</sup> See: Duhamel M, Mo K, Edwards EA. 2004. Characterization of a Highly Enriched Dehalococoides-Containing Culture That Grows on Vinyl Chloride and Trichloroethene. *Applied and Environmental Microbiology*. 5538-5545. DOI: 10.1128/AEM.70.9.5538-5545.2004.

<sup>140</sup> Stroo HF, Ward CH. 2010. *In Situ Remediation of Chlorinated Solvent Plumes*. Springer Science & Business Media.

**B. Over-reliance on qualitative assessments of TCE partitioning in the environment means EPA has failed to adequately address risks to terrestrial and sediment-dwelling organisms.**

Despite having environmental monitoring data that indicate that TCE is present in air, soil and sediment and will likely expose terrestrial and sediment-dwelling organisms, EPA instead relied exclusively on qualitative and screening-level assessments to minimize such impacts.

- i. TCE exposures to terrestrial organisms can occur through multiple pathways of exposure.*

EPA has ignored important pathways of TCE exposure to terrestrial organisms, justifying its lack of a quantitative assessment of exposures to terrestrial organisms because "TCE is not expected to partition to soil but is expected to volatilize to air, based on its physical-chemical properties" (p. 275). This is despite finding potential hazard based on reviewed data (p. 275 and in the Problem Formulation, pp. 40-41).

Importantly, this statement ignores entirely TCE exposures to terrestrial organisms through air, which is a primary pathway of exposure to TCE. EPA dismisses exposure to terrestrial organisms from the ambient air pathway based on the unsupported argument that such exposures are adequately managed by the Clean Air Act (p. 276); see section 2.B. for our comments on the many concerns with this argument.

Additionally, EPA is ignoring exposures to terrestrial organisms that may occur from contaminated water and soil. EPA must comprehensively consider all routes of exposure to terrestrial organisms in its risk evaluation of TCE given its widespread detection throughout the environment including at contaminated sites.

In addition to the fact that nearly two million pounds<sup>141</sup> of TCE are released annually into the air, due to its volatility, disposal to water and land may also create a route of exposure to organisms living at the water-atmosphere or water-soil interface (e.g., amphibians, birds and shorebirds, and burrowing organisms). These organisms may be significantly impacted by TCE exposure.

EPA needs to provide a rational and clear analysis based on the best available science and reasonably available information to support its conclusions, and at this point, it has failed to do so.

- ii. Impacts on sediment dwelling organisms need to be evaluated.*

For sediment-dwelling organisms, EPA stated in its problem formulation:

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<sup>141</sup> 2018 TRI Data, <https://www.epa.gov/toxics-release-inventory-tri-program/tri-data-and-tools>.

No data on the toxicity to sediment organisms (e.g. *Lumbriculus variegatus*, *Hyalella azteca*, *Chironomus riparius*) were found; however, \*\*\* TCE is not expected to partition to sediment, based on physical chemical properties. (p.41)

Absence of hazard data does not equate to absence of hazard. A cursory review of the literature identified a study that found sensitivity of nematodes (sediment-dwelling organisms) to TCE at concentrations of 1 ug/ml (or 1000 ppb).<sup>142</sup> At 30 mg/L, the researchers reported a significant reduction in the nematode maturity index, described as an index of diversity based on trophic groupings in nematodes in riparian soil microcosms. As noted previously (section 6.A.ii.), TCE has been measured in the sediment at concentrations of up to 26,000 ug/kg (or 26,000 ppb). Therefore, dismissing sediment exposure as a potential impact is clearly unwarranted.

The scope of the draft risk evaluation limited the COUs included to those with applicable occupational exposure scenarios (OES). EPA then appears to have illogically limited its evaluation of risks to environmental receptors to just these COUs (p. 46). Furthermore, EPA disregarded data associated with contaminated sites from its water monitoring data ("Data Filtering and Cleansing," p. 89) and excluded monitoring data potentially impacted by Superfund sites in its watershed analysis ("Geospatial Analysis Approach," p. 89).

**C. EPA cannot ignore environmental releases of a chemical because it cannot attribute each release to a particular condition of use.**

EPA has indicated that “only a few USGS-NWIS and STORET monitoring stations aligned with the watersheds of the TCE-releasing facilities *identified under the scope* of this assessment, and the co-located monitoring stations had samples with concentrations below the detection limit; therefore, *no direct correlation* can be made between them” (p. 98, emphases added). This language suggests EPA may believe it must be able to attribute every environmental release of a chemical to a particular condition of use or facility in order to consider its risks in a risk evaluation. This is not the case.

Nothing in TSCA allows EPA to ignore data simply because they have not been tied to a particular condition of use, let alone a particular facility. EPA must conduct risk evaluations under TSCA that consider all “reasonably available” information relating to a chemical substance, including information that may not be tied to specific conditions of use. 15 U.S.C. § 2625(k). EPA’s rules further define “reasonably available information” as “information that EPA possesses or can reasonably generate, obtain and synthesize for use \*\*\*.” 40 C.F.R. §§ 702.3, 702.33.

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<sup>142</sup> Fuller ME, Scow KM, Lau S, Ferris H. 1997. Trichloroethylene (TCE) and toluene effects on the structure and function of the soil community. *Soil Biology and Biochemistry*. 29(1):75–89. doi:[10.1016/S0038-0717\(96\)00247-7](https://doi.org/10.1016/S0038-0717(96)00247-7).

Data that cannot be attributed to specific conditions of use are still relevant to determining whether *the chemical substance* presents an unreasonable risk, and as such must be considered by EPA. EPA cannot ignore data simply because it has not determined or even cannot determine how much of the exposure is attributable to a particular condition of use. Such a consideration may be more relevant at any subsequent risk management stage, when EPA may need to understand the extent to which specific measures will reduce exposure and risk. But that future need provides no basis for EPA to ignore risk-relevant information at the risk evaluation stage.

**D. EPA's analysis of aquatic risks may underestimate the risk.**

*i. EPA's concentration of concern (COC) for algae does not pass muster.*

As explained more in section 7.B., EPA's own analyses showed that TCE presents an unreasonable risk to aquatic organisms (pp.354, 378-379). Specifically, EPA found that releases from certain disposal and recycling facilities would result in surface water concentrations well above the concentrations of concern (COC) for TCE (pp. 260-263). But if anything, EPA's analysis may have underestimated the risk from these releases especially for algae.

EPA calculated a COC for algae of 52,000 ppb (52 mg/L) using species sensitivity distribution (SSD), justifying it as being representative for algae species "as a whole" (p. 194). EPA determined that "as a whole" in this case constitutes nine species of algae. Yet algae are an incredibly diverse (and poorly defined) group of organisms that represent 15 phyla and 54 classes; estimates of total species of algae are between 72,000 and 1 million.<sup>143</sup>

To conclude that a COC of 52 mg/L is protective of algae "as a whole," based on only nine species, with a concentration that is over 17,000 times higher<sup>144</sup> than the COC EPA derived for the most sensitive species of algae identified for the draft risk evaluation is indefensible. Instead, EPA should use the most sensitive species as its indicator organism to develop appropriately protective COCs.

Using the far more appropriate COC of 3 ppb, EPA identified risks from exposure to TCE to the most sensitive algae specie at 521 facilities (p. 354); nevertheless, EPA dismissed these RQs as actually showing no risk for "algae species as a whole" based on its questionably calculated COC (pp. 378-379).

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<sup>143</sup> Guiry MD. 2012. How many species of algae are there? *Journal of Phycology*. 48(5):1057–1063. doi:10.1111/j.1529-8817.2012.01222.x.

<sup>144</sup> See p. 199. The algal COC derived by EPA for TCE is 3 ppb; the algal HC<sub>05</sub> (Hazardous Concentration threshold for 5% of species) derived by EPA is 52,000 ppb, a 17,000-fold difference.

*ii. EPA based its exposure estimates on unreliable surface water concentrations uncertain calculations.*

As discussed previously (see section 6.C.), not only did EPA ignore environmental impacts to surface water from TCE discharges, the existing surface water data may not be representative of TCE concentrations. EPA acknowledges the limitations of data in the USGS-NWIS and STORET databases, stating "the monitoring studies used to collect the data were not specifically designed to evaluate TCE distribution across the US," and "it is unclear whether the data are representative of other locations in the US" (p. 98). EPA goes on to note that these data "cannot be interpreted as reflecting concentrations downstream of direct release sites, which could be higher than reported measured levels" (p. 98).

When calculating surface water release estimates, EPA correctly states that "release estimates serve as the key inputs into the exposure mode and are therefore a key component of the overall aquatic exposure scenario confidence" (p. 98). Based on available data, and other considerations relating to the estimation of rates of discharges from various facilities – including outdated stream flow data in EFAST, some of which are decades old<sup>145</sup> – EPA was over-generous in assigning a "moderate" confidence in wastewater discharge estimates (p. 98).

Furthermore, EPA applied a wastewater treatment removal rate of 81% to all indirect releases, as well as to direct releases from WWTPs (p. 85 and footnote b of Table 4-1). EPA did not establish that this assumed removal actually occurs, so EPA may be underestimating the total risk presented by releases from these facilities.

## **7. EPA's unreasonable risk definition and risk determinations are severely flawed.**

### **A. EPA grossly underestimates occupational risk, leading to 'no unreasonable risk' findings or understatements of the extent and magnitude of the unreasonable risks it does find.**

EPA underestimates occupational risks in three major ways in its draft risk evaluation:

1. EPA assumes that workers will wear fully effective personal protective equipment (respirators and gloves) in most scenarios and relies on that assumption to avoid finding that its risk estimates represent unreasonable risk or to understate the extent and magnitude of the risk. See section 5.A. and subsection i. below for the details.
2. EPA finds a cancer risk to workers unreasonable only if it exceeds a level of 1 in 10,000 – which is as much as 100 times higher a risk than warrants regulation under

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<sup>145</sup> See p. 98. Despite having access to newer hydrological data, EPA used the stream flow data in EFAST, which are 15 to 30 years old.

TSCA to protect workers and other vulnerable subpopulations. See subsection ii. below for the details.

3. For ONUs EPA has failed to identify unreasonable risks for the most highly exposed, and hence most vulnerable, basing its ONU risk determinations exclusively on central tendency exposure estimates. See subsection iii. below for the details.

The effect of each of these decisions is to underestimate occupational risk – ultimately either leading EPA to determine “no unreasonable risk” or to grossly understate the extent and magnitude of the unreasonable risks it does find. Below we discuss each of these issues in further detail.

- i. By assuming use of PPE, EPA conflates risk evaluation and risk management and significantly understates risk.*

TSCA intentionally divides risk evaluation and risk management into two distinct processes, whereby regulatory measures are to be considered *after* EPA finds an unreasonable risk. However, by choosing to make risk determinations based on an assumption of PPE, EPA conflates risk evaluation and risk management and leads EPA either not to find an exposure presents unreasonable risk, or more commonly, to underestimate the extent and magnitude of TCE’s risk under many scenarios (see section 5.A.). EPA’s failure to make an unreasonable risk determination based on its PPE assumption could potentially deny itself the opportunity to impose mandatory requirements sufficient to control workplace exposures.

For example, Table 4-54 (pp. 358-369) demonstrates that for non-cancer risk from acute dermal exposure, EPA has actually found excessive risk in the absence of glove use in *every* occupational scenario it examined. EPA had to assume use of gloves in order not to find excessive risk under most central tendency exposure scenarios. Thus, when it comes to the risk determinations, EPA makes almost no unreasonable risk determinations based on central tendency dermal exposures, invoking PPE (section 5.3). EPA’s failure to identify that central tendency dermal exposures can lead to unreasonable risk in the absence of PPE could constrain its authority to require that the gloves it assumed are used will actually be used.

See EDF’s further critique of EPA’s assumption of PPE use in the workplace in sections 1.B. and 5.A.

- ii. EPA’s use of a 1 in 10,000 cancer risk level as reasonable for workers is deeply flawed.*
  - a. EPA’s approach must be rejected on scientific as well as legal grounds.*

EPA has proposed to establish  $1 \times 10^{-4}$  as the cancer risk benchmark for workers (p. 376). EPA cites NIOSH guidance and the *Benzene* decision for support (p. 376, footnote 22), but that

guidance and that case pertain to how the standard for health protection is applied under OSHA, 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. 374, footnote 20).

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  $1 \times 10^{-4}$  benchmark (p. 376, footnote 21).

Indeed, EPA's reliance on the *Benzene* decision cannot be reconciled with the statutory differences between OSHA's standard and TSCA's unreasonable risk standard. In the *Benzene* case, the Court interpreted a provision of the OSH Act that defined standards as "reasonably necessary or appropriate to provide safe or healthful employment and places of employment," as requiring OSHA "to make a threshold finding that a place of employment is unsafe—in the sense that *significant* risks are present and can be eliminated or lessened by a change in practices." *Indus. Union Dep't, AFL-CIO v. API*, 448 U.S. 607, 642 (D.C. Cir. 1980) (emphasis added). The Court's interpretation turned on the statutory language of the OSH Act, the Act's structure, and its legislative history. But EPA can point to *no* statutory language in TSCA invoking this standard, EPA has pointed to no similarities between the two statute's structures, nor has EPA pointed to any legislative history suggesting that TSCA adopted the OSH Act's standard. Moreover, if Congress had intended to adopt the *Benzene* standard under TSCA, it would have required that EPA regulate "significant risks," not "unreasonable risks." Indeed, the significant differences between the language and structure of the two statutes strongly indicates that Congress meant to adopt a different standard in TSCA, not the standard articulated by the Court in the *Benzene* case.

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  $1 \times 10^{-6}$  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). Nor does EPA only apply this standard under the Clean Air Act. When setting Clean Water Act criteria, “EPA intends to use the  $10^{-6}$  risk level, which the Agency believes reflects an appropriate risk for the general population. EPA’s program office guidance and regulatory actions have evolved in recent years to target a  $10^{-6}$  risk level as an appropriate risk for the general population. EPA has recently reviewed the policies and regulatory language of other Agency mandates (e.g., the Clean Air Act Amendments of 1990, the Food Quality Protection Act) and believes the target of a  $10^{-6}$  risk level is consistent with Agency-wide practice.”<sup>146</sup> When Congress amended TSCA to include the unreasonable risk standard, it did so knowing that agency practice was to regulate cancer risks at the  $10^{-6}$  risk level. It should be presumed that Congress meant to adopt this risk standard when codifying the unreasonable risk standard.

In grasping for support for its approach in this risk evaluation by citing other mentions by EPA of the  $1 \times 10^{-4}$  risk level (p. 376, footnote 21), 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. 426 n. 22, 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*.<sup>147</sup>

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<sup>146</sup> U.S. EPA, *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* p. 2-6 (2000), <https://www.epa.gov/sites/production/files/2018-10/documents/methodology-wqc-protection-hh-2000.pdf>.

<sup>147</sup> 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 Nov. 26, 2019).

But in this draft 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 a number of conditions of use of methylene chloride 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.

*b. EPA's approach leads to a major understatement of the extent of unreasonable risk workers and ONUs face from TCE exposure.*

EPA's occupational risk estimates were significantly impacted by EPA's selection of  $10^{-4}$  as the cancer risk benchmark. The impact is less than in draft risk evaluations for other chemicals only because EPA's identified cancer risk even exceeds its lax benchmark for most scenarios it examined. Nonetheless, EPA failed to identify the cancer risk as unreasonable in a number of cases, and it of course effectively understates the magnitude of the cancer risk even where it identified it as unreasonable.

To determine how large the impact is, EDF examined EPA's cancer risk estimates to workers for each of the combinations of industrial/commercial COUs, exposure routes (inhalation or dermal) and exposure levels (high-end or central tendency) presented in Table 4-54. Our analysis is provided in the Excel file submitted as Appendix 4 along with these comments.

While EPA applied a  $10^{-4}$  cancer risk benchmark to these estimates, EDF looked at whether they exceed a cancer risk benchmark of  $10^{-5}$  or  $10^{-6}$  and should have at least potentially been identified as presenting an unreasonable risk to workers.

In the 91 cases where EPA assumed use of respirators, EPA identified 79 as exceeding its  $10^{-4}$  cancer risk benchmark. Had EPA used a benchmark of  $10^{-5}$  or  $10^{-6}$ , EPA would have identified as unreasonable an additional 11 and 12 of the 91 cases, respectively. Equally important, even for those cases EPA identified as presenting unreasonable risk, use of the more appropriate benchmark would have established the need to reduce exposure to TCE to at least a 10-fold lower level by subsequent regulation of TCE to eliminate the unreasonable risk EPA has identified.

*iii. EPA's assumption that ONUs are never exposed at levels above the central tendency estimates it derives for workers is flawed.*

For COUs where EPA states it has no basis to distinguish between worker and ONU exposures, it reports for ONUs only the risk associated with its central tendency estimate for workers and provides no estimate of high-end risk for ONUs. These cases are those where the "population" column in Table 4-54 identifies the population as "ONU (upper limit)." EPA then determines

ONUs face an unreasonable risk only if its central tendency risk estimate for workers (carried over to ONUs) exceeds its benchmark.

EPA states:

For some conditions of use, EPA did not separately calculate risk estimates for ONUs and workers. For these conditions of use, there is uncertainty in the ONU risk estimates since the data or modeling did not distinguish between worker and ONU inhalation exposure estimates. ONU inhalation exposures are expected to be lower than inhalation exposures for workers directly handling the chemical substance; however, the relative exposure of ONUs to workers in these cases cannot be quantified. To account for this uncertainty, EPA considered the central tendency risk estimate when determining ONU risk for those conditions of use for which ONU exposures were not separately estimated. (p. 35)

Among other concerns, EPA has provided no empirical basis at all for its therefore-arbitrary assumption that ONUs will never be exposed at levels higher than the central tendency exposure workers experience. 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. EPA represents its high-end estimates as "generally intended to cover individuals or sub-populations with greater exposure," while its central tendency estimates apply to the "average or typical exposure" that people experience (p. 375). TSCA would not permit EPA to protect against only the "average or typical exposure;" in fact, when it comes to workers, ONUs, and other "potentially exposed or susceptible subpopulations," EPA is required to protect all of them.

*iv. EPA has dismissed unreasonable risk based on biased assessment of exposure estimates.*

Epidemiological and exposure assessment studies have the potential to either under- or over-estimate exposure, depending on the methods and approaches utilized. For this reason, it is important to consider data from the entire body of evidence rather than any particular study alone. Yet, in attempting to downplay its unreasonable risk determinations for TCE, the Agency has chosen only to emphasize the potential for data sources to *overestimate* exposure. EPA states:

Additionally, some data sources may be inherently biased. For example, bias may be present if exposure monitoring was conducted to address concerns regarding adverse human health effects reported following exposures during use. These sources may cause exposures to be overestimated. (p. 348)

This one-sided statement, emphasizing only those factors tending to overestimate exposure while ignoring the potential for similar factors to underestimate exposures, highlights the Agency's bias evident in this draft risk evaluation.

**B. EPA cannot reasonably dismiss its findings of environmental risk merely by invoking uncertainty.**

For environmental risk, EPA's own analyses showed that TCE presents an unreasonable risk to aquatic organisms (pp.354, 378-379), but EPA dismisses this unreasonable risk by invoking "uncertainty" (p. 379), which is reflective of EPA limiting its analysis to only a "qualitative consideration of the physical-chemical and fate characteristics" as well as conditions of use (pp. 31, 378-379). Beyond this weak assertion and the accompanying distortion of its own findings with respect to environmental risk, EPA provides no basis for its dismissal of identified risks.

EPA used a Risk Quotient (RQ) to compare environmental concentration to the effect level to characterize the risk to aquatic organisms. (p. 31). Under this approach, "[i]f the RQ is greater than 1, the exposure is greater than the effect concentration and there is potential for risk presumed." (p. 376). Risks to the most sensitive species of algae were identified near 521 facilities (with 20 days or more of exceedances for 461 of these facilities, and more than 100 days exceedances for 10 facilities).

Thus, based on EPA's own analyses, EPA found risks to aquatic organisms from 521 facilities (p. 354), with the RQ exceeding 1 (in one case exceeding the COC by 1,000-fold) (p. 261), but EPA dismissed this risk merely by invoking uncertainty and relying on a dubiously calculated COC for algae (see section 6.D.i.). This approach is arbitrary and capricious because EPA refuses to accept the outcomes of its own analyses, and EPA's conclusions run contrary to the evidence before the agency. Based on the analysis presented in the draft risk evaluation, EPA should find an unreasonable risk to the environment presented by certain conditions of use.

In summarizing its risk conclusions, EPA states that: "Risk to the most sensitive species of algae were identified near 521 facilities (with 20 days or more of exceedances for 461 of these facilities, and more than 100 days exceedances for 10 facilities)." (p. 354). But EPA then does not make risk findings. Instead—in addition to the wholesale dismissal of potential risks to the most sensitive algae species—in the risk characterization section, EPA states that:

For aquatic organisms like aquatic invertebrates and fish, one facility had an acute RQ greater than 1 (RQ = 3.11) \*\*\* Another facility had an acute RQ of 0.94 indicating some uncertainty about whether it would also pose risks to aquatic organisms from acute exposures. \*\*\* Both facilities had chronic RQs greater than 1, exceeding the chronic COC of 788 ppb for 20 days. \*\*\* Monitored data from literature showed some exceedances of the algae COC of 3 ppb in ambient water; however, the data show no

exceedances of the algae COC of 52,000 ppb. Therefore, EPA did not identify risks for acute or chronic exposure durations in ambient water for areas where monitored data were reasonably available. Given the uncertainties in the modeling data and exceedance of the acute RQ for only one data point and of the chronic RQ for only two out of 70 facilities modeled, EPA does not consider these risks unreasonable (see Section 4.5.2). (pp. 378-379)

EPA essentially acknowledges that it did find unreasonable risk for some conditions of use, and EPA then dismisses that risk on the basis of “uncertainties in the data” and on selective monitoring data that exclude contaminated environments and ranged across five orders of magnitude (above 3 ppb but below 52,000 ppb).<sup>148</sup> Notably, EPA provides no cogent explanation of what uncertainties exist in the data. Moreover, to the extent there are uncertainties in EPA’s analysis, such uncertainties counsel in favor of a finding of unreasonable risk – EPA could as easily be underestimating the risk presented by these conditions of use as overestimating them. Uncertainty increases the chances of an unreasonable risk; it does not diminish them. Uncertainty, standing alone, does not justify a finding of no unreasonable risk when EPA’s own analyses support a finding of unreasonable risk.

To be clear, for one of these facilities, the exceedances EPA calculated were far in excess of the relevant concentration of concern. That facility, according to EPA, had “a chronic RQs of 3.81 with 20 days of exceedance, and an algae COCs representing the most sensitive species of algae of 1,000 with 20 days of exceedance. In other words, the surface water concentration modeled for this facility was 3.81 times higher than the COC for chronic exposures, and 1,000 times higher than the COC for the most sensitive species of algae. Assuming 260 days of releases from the facility, the algae RQ representing the most sensitive species was 56.33 with 350 days of exceedance.” (pp. 260-261).

### **C. EPA’s analysis of distribution in commerce should be clarified and made explicit.**

In the draft risk evaluation, EPA states that “distribution in commerce” “presents an unreasonable risk of injury to health (workers and occupational non-users),” (p. 391), but the draft risk evaluation does not describe the analysis supporting this finding. EPA states that a “quantitative evaluation of the distribution of TCE was not included in the risk evaluation because exposures and releases from distribution were considered within each condition of use.”

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<sup>148</sup> For context, other TCE toxicity thresholds that fall between 3 ppb and 52,000 ppb (52 ppm) include the LC50 for fish (between 28 and 66.8 mg/L) and acute toxicity for aquatic invertebrates (7.8 mg/L) see Table 3.1 p. 193). Hence concentrations that would not exceed EPA’s asserted algae COC of 52,000 ppb would be *highly lethal to fish* and *highly acutely toxic to aquatic invertebrates*.

(p. 391). In truth, EPA did not prepare even a *qualitative* evaluation of distribution in commerce of TCE. Based on our search of the draft risk evaluation and supplemental documents, nowhere does it appear EPA actually analyzed distribution in commerce, and EPA should clarify how it analyzed this condition of use and provide the basis for its finding of unreasonable risk.

EPA states that it analyzed distribution in commerce when analyzing the other conditions of use. (pp. 391, 48). But when examining EPA’s analysis of various conditions of use—for example, Occupational Exposures—EPA does not appear to have actually analyzed the distribution in commerce of TCE as it relates to these other conditions of use. (pp. 100-107). We could not find any discussion in the analysis of the other conditions of the use that actually addressed distribution in commerce as an aspect of those conditions of use.

Nonetheless, EPA finds that distribution in commerce presents an unreasonable risk. (p. 391). This finding makes sense in light of EPA’s conclusion that the other conditions of use present an unreasonable risk (pp. 379-383). If EPA really did analyze distribution of commerce when analyzing these other conditions of use, then the finding of unreasonable risk on these other conditions of use would seem to extend to distribution in commerce. Nonetheless, EPA should clarify how it analyzed distribution and the basis for its finding of unreasonable risk.

In addition, the draft risk evaluation and problem formulation give no attention to potential releases and exposures resulting from accidental releases. EDF does not suggest that EPA needs to consider every possible scenario, but the risk of accidental releases and exposures is very real and certainly “reasonably foreseen” in many respects. For example, as and after Hurricane Harvey passed through Houston, over 40 sites released toxic chemicals into the environment.<sup>149</sup> Given the known accidental releases, the huge number of petrochemical plants and refineries in the Houston area, and the likelihood that flooding there may become more common in light of climate change, such events are clearly reasonably foreseen and hence EPA needs to give more consideration to the potential for accidental releases.

## 8. Systematic review issues

### A. OPPT provides neither explanation nor empirical support for its revisions to the systematic review data quality criteria for epidemiological studies, which make it difficult for epidemiological studies to be scored as overall as high quality.

EPA applied its Office of Pollution Prevention and Toxics’ (OPPT) updated data quality criteria to epidemiological studies in this draft risk evaluation. The completed data quality evaluation

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<sup>149</sup> See, e.g., *More Than 40 Sites Released Hazardous Pollutants Because of Hurricane Harvey*, N.Y. TIMES (Sept. 8, 2017), [https://www.nytimes.com/interactive/2017/09/08/us/houston-hurricane-harvey-hazardous-chemicals.html?\\_r=0](https://www.nytimes.com/interactive/2017/09/08/us/houston-hurricane-harvey-hazardous-chemicals.html?_r=0).

for these studies was provided in the Systematic Review Supplemental File.<sup>150</sup> EPA OPPT provide neither an 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. EPA OPPT’s scoring methodology is already at odds with best practices in systematic review, see our earlier comments on OPPT’s Application of Systematic Review in TSCA Risk Evaluations,<sup>151</sup> 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.

Further, at least six metrics in EPA OPPT’s updated epidemiological criteria can no longer receive a score of High, including Metric 5 (Exposure Levels) and Metric 15 (Statistical Models). Since these individual metrics can at best be rated as Medium (a change from the earlier epidemiological criteria), epidemiological studies are thus less likely to be considered high quality overall and as a result may be given more limited consideration than other types of evidence (animal and *in vitro* studies), where it remains possible to score High across every data quality metric.

In addition to issues with individual scoring criteria, the scheme used to calculate the overall rating for a particular study is not clearly presented in either the updated criteria document or the completed evaluation. The following equation is presented for calculating the overall rating:<sup>152</sup>

\* MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left[ \frac{\sum_i (\text{Metric Score}_i \times \text{MWF}_i)}{\sum_j \text{MWF}_j} \right]_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases}$$

where High  $\geq 1$  to  $< 1.7$ ; Medium  $\geq 1.7$  to  $< 2.3$ ; Low  $\geq 2.3$  to  $\leq 3.0$ . If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

The subscripts of *i* and *j* are not defined, and the final subscript of *0.1* is not explained. From this description, it is not possible to see how EPA OPPT calculated its overall ratings for these studies.

<sup>150</sup> U.S. EPA, *Systematic Review Supplemental File: TCE Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Studies CASRN: 75-09-2* p. 5 (Oct. 2019), [https://www.epa.gov/sites/production/files/2020-02/documents/15\\_tce-data\\_quality\\_evaluation\\_of\\_human\\_health\\_hazard\\_studies\\_-\\_epidemiological\\_data.pdf](https://www.epa.gov/sites/production/files/2020-02/documents/15_tce-data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_data.pdf).

<sup>151</sup> EDF Comment on EPA’s Systematic Review, <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0077>.

<sup>152</sup> U.S. EPA, *Systematic Review Supplemental File: TCE Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Studies CASRN: 75-09-2* p. 5 (Oct. 2019), [https://www.epa.gov/sites/production/files/2020-02/documents/15\\_tce-data\\_quality\\_evaluation\\_of\\_human\\_health\\_hazard\\_studies\\_-\\_epidemiological\\_data.pdf](https://www.epa.gov/sites/production/files/2020-02/documents/15_tce-data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_data.pdf).

Given the concerns related to the appropriateness of the OPPT tool for epidemiological studies and the effect of its application in the context of TCE, the agency should consider other study evaluation tools that are more appropriate for the consideration of the quality of observational epidemiologic studies. Examples include the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) tool<sup>153</sup> and the Navigation Guide.<sup>154</sup>

**B. OPPT’s approach taken to evidence integration in the draft TCE 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,<sup>155</sup> 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.<sup>156</sup>

As noted in the 2014 National Academy of Sciences (NAS) report that reviewed EPA’s IRIS program:

Critical elements of conducting a systematic review include formulating the specific question that will be addressed (problem formulation) and *developing the*

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<sup>153</sup> Dekkers, Olaf M., et al. "COSMOS-E: guidance on conducting systematic reviews and meta-analyses of observational studies of etiology." *PLoS medicine* 16.2 (2019).

<sup>154</sup> Woodruff, Tracey J., and Patrice Sutton. "The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes." *Environmental health perspectives* 122.10 (2014): 1007-1014.

<sup>155</sup> Environmental Defense Fund Comments on Application of Systematic Review in TSCA Risk Evaluations (Aug. 16, 2018), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0077>; 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) (Jan. 14, 2019), <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0013>.

<sup>156</sup> See 40 C.F.R. 702.33 Definition of “Weight of scientific evidence,” <https://www.law.cornell.edu/cfr/text/40/702.33>.

*protocol* that specifies the methods that will be used to address the question (protocol development).<sup>157</sup>

After the systematic-review questions are specified, protocols for conducting the systematic reviews to address the questions should be developed. *A protocol makes the methods and the process of the review transparent, can provide the opportunity for peer review of the methods, and stands as a record of the review.* It also minimizes bias in evidence identification by ensuring that inclusion of studies in the review does not depend on the studies' findings. Any changes made after the protocol is in place should be transparent, and the rationale for each should be stated. EPA should include protocols for all systematic reviews conducted for a specific IRIS assessment as appendixes to the assessment.<sup>158</sup>

EPA's IRIS program reflects this NAS recommendation by developing problem formulation and assessment protocols for each of its assessments.<sup>159</sup> OPPT needs to develop full protocols for each of its risk evaluation and should consult with the IRIS program on how best to do so in consideration of requirements under TSCA.

### **C. EPA's selective inclusion of studies otherwise excluded as part of its systematic review process raises concern around inconsistency and bias**

At various points in the draft risk evaluation, EPA chooses to include studies that were otherwise excluded through the agency's systematic review process, and in doing so raises concerns about inconsistency and bias.

For example, in Section 3.2.1 (Approach and Methodology description for the evaluating Human Health Hazards), EPA notes that "[i]nformation from studies that were rated unacceptable were only discussed on a case-by-case basis for hazard ID and weight-of-scientific-evidence assessment but were not considered for dose-response analysis." (p. 202) Setting aside its significant flaws (see section 8.A. and 8.B.) the TSCA Systematic Review Method leads EPA to rate a study as unacceptable when one or more data quality metrics for that study are scored as unacceptable. A metric score of unacceptable means that "[s]erious flaws are noted in the domain metric that consequently make the data/information source unusable." Per the TSCA Systematic Review Method studies rated unacceptable, are "...disqualified from further consideration...."

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<sup>157</sup> Nat'l Research Council, *Review of EPA's Integrated Risk Information System (IRIS) Process* (2014) at p. 5, <https://www.ncbi.nlm.nih.gov/books/NBK230060/> (emphasis added).

<sup>158</sup> *Id.* at 6 (emphases added).

<sup>159</sup> U.S. EPA, Office of Research & Dev., National Academy of Science Committee to Review Advances Made to the IRIS Program at slide 23 (Feb. 2018), <http://nas-sites.org/dels/files/2018/01/AdIRIS-15.pdf>.

In the context of the draft risk evaluation, EPA fails to identify which “unacceptable” studies were referenced for hazard identification and weight-of-the-scientific-evidence assessment, for which endpoints, and on what basis. Absent any explanation, let alone guidance, for when and how “unacceptable” studies may be considered during risk evaluation, EPA’s use ad hoc use of unacceptable studies introduces significant risk for arbitrary, biased, and inconsistent treatment of scientific evidence.

Similarly, footnote 15 in section 3.2.1 (p. 202) indicates that “some of the studies that were excluded based on the PECO statement were considered later during the systematic review process as needed. For example, EPA reviewed mode of action information to qualitatively support the health hazard assessment.” While referencing mechanistic information during hazard identification is reasonable, EPA’s use of studies here that are otherwise excluded through the PECO statement again raises concern that EPA has introduced bias and inconsistency in the risk evaluation process.

EPA should develop general guidance for when these allowances may be considered, and clearly identify, with supporting justification, those specific instances where studies excluded during systematic review or other processes can be referenced and relied on in developing the risk evaluation.

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