american cleaning institute®

December 14, 2023

Via E-Mail

Information Quality Guidelines Staff
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., N.W. (Mail Code 28221T)
Washington, DC, 20460

Re: Request for Correction of Information under the Information Quality Act: The Toxic Substances Control Act (TSCA) Risk Evaluation for 1,4-Dioxane

Dear Sir or Madam:

The American Cleaning Institute® (ACI) and the American Chemistry Council (ACC) submit this request for correction of information (RFC) on the final "*Risk Evaluation for 1,4-Dioxane CASRN: 123-91-1*" (Final 1,4-DX RE) issued by the U.S. Environmental Protection Agency's (EPA) Office of Pollution Prevention and Toxics (OPPT) in December 2020.[1] This RFC is submitted under the Information Quality Act (IQA) and the implementing guidelines issued by the Office of Management and Budget (OMB) and EPA.[2,3,4] The focus of this RFC is on OPPT's decision to utilize a linear low-dose extrapolation (*i.e.*, no threshold) for assessing potential

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1 EPA (2020a) *Final Risk Evaluation for 1,4-Dioxane CASRN: 123-91-1*, EPA Document # EPA-740-R1-8007, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency (EPA), available at https://www.epa.gov/sites/default/files/2020-12/documents/1._risk_evaluation_for_14-dioxane_casrn_123-91-1.pdf.

2 44 U.S.C. § 3516, available at https://www.govinfo.gov/content/pkg/USCODE-2008-title44/pdf/USCODE-2008-title44-chap35-subchapI-sec3516.pdf.

3 EPA (2002a) *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Republication* Agency: Office of Management and Budget, Executive Office of the President, Action: Final Guidelines, FEDERAL REGISTER, Vol. 67, pp. 8452-8460 (Feb. 22, 2002) available at https://www.govinfo.gov/content/pkg/FR-2002-02-22/pdf/R2-59.pdf.

4 EPA (2002b) *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency*, EPA/260R-02-008 (Oct. 2002), available at https://www.epa.gov/sites/default/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf.

carcinogenic risks from exposures to 1,4-DX. OPPT justified this approach because, according to OPPT, the carcinogenic "mode of action (MOA) is unknown or unclear."[5]

For the reasons discussed below, the Agency's Risk Evaluation's findings are scientifically flawed and we request that the Evaluation's conclusions be withdrawn so they may be carefully reassessed and corrected.[6] This Request for Correction is appropriately submitted pursuant to the IQA, EPA's implementing guidelines, and those of OMB, because: (a) the conclusions reached under the Risk Evaluation constitute "information" which the Agency has "disseminated" publicly; (b) the Risk Evaluation, by definition, will (unless withdrawn) be "influential" as it will inform a TSCA Risk Management rule; and (c) changes are required to ensure the Risk Evaluation meets the Agency's own data quality and scientific standards including those required by Section 26 of TSCA (it must use the "best available science" and employ a weight of the evidence approach).

We specifically request that OPPT withdraw its Risk Evaluation and reexamine its conclusion with regard to carcinogenicity taking into consideration conclusions reached by other regulatory agencies around the world that have determined that the carcinogenic MOA for 1,4-DX supports application of a non-linear approach (*i.e.*, a threshold). For example, the Commonwealth of Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) concluded in 1998 that "Overall, indications are that the primary mechanism(s) of tumourigenicity for 1,4-dioxane in animals is non-genotoxic" and that "Evidence from animal studies indicates the existence of a threshold dose for toxicity and carcinogenicity at doses where 1,4-dioxane metabolism becomes saturated."[7] The European Chemicals Bureau (ECB) came to the same conclusion in its 2002 *European Union Risk Assessment Report* stating that "1,4-Dioxane is considered to be a carcinogen acting by a non-genotoxic mode of action. Therefore, a threshold approach is appropriate."[8] More recently, Health Canada concluded in its 2021 *Guideline*

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5 EPA (2020a), *supra* note 1, at 186.

6 A timely withdraw of the 2020 Risk Evaluation is especially appropriate, given the Agency should reconsider its assessment and conclusions upon receipt of the recent Peer Review by EPA's own Science Advisory Committee on Chemicals.

7 NICNAS (1998) *1,4-Dioxane Priority Existing Chemical No. 7*, Full Public Report, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 129 pp., at 61, available at https://www.industrialchemicals.gov.au/sites/default/files/PEC7-1-4-Dioxane.pdf.

8 ECB (2002) *European Union Risk Assessment Report, 1,4-Dioxane, CAS No. 123-91-1, EINECS No. 204-661-8*, Institute for Health and Consumer Protection, European Chemicals Bureau (ECB), 2nd Priority List, Vol. 21, 142 pp., at 91, available at https://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa.

Technical Document for Public Consultation on 1,4-Dioxane in Drinking Water that "Since 1,4-dioxane acts through a non-genotoxic MOA and demonstrates dose-related non-linear kinetics, a non-linear (threshold) risk assessment approach is considered appropriate."[9] Further, the European Chemicals Agency's (ECHA) Committee for Risk Assessment (RAC) concluded in its 2022 *Opinion on Scientific Evaluation of Occupational Exposure Limits for 1,4-Dioxane* that "A non-linear (threshold) risk assessment approach is considered appropriate."[10] EPA does not explain why it has departed from the scientific conclusions of these other competent authorities. As discussed more fully below, this departure alone is a serious weakness in OPPT's 2020 Final 1,4-DX RE yet one that EPA has perpetuated in subsequent assessments on 1,4-DX.[11]

Below, we provide detailed information on the basis for this RFC within the context of the information EPA requires for these types of submissions.

1. Name and contact information for the individual or organization submitting a complaint; identification of an individual to serve as a contact.

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9 Health Canada (2021) *Guidelines for Canadian Drinking Water Quality Guideline Technical Document 1,4-Dioxane*, 63 pp., at 39-40, available at https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-1-4-dioxane/1-4-dioxane-pdf-eng.pdf.

10 ECHA (2022a) *Committee for Risk Assessment, RAC, Opinion on Scientific Evaluation of Occupational Exposure Limits for 1,4-Dioxane*, ECHA/RAC/OEL-O-0000007101-89-01/F 18/03/2022, European Chemicals Agency (ECHA), 10 pp., at 8, available at https://echa.europa.eu/documents/10162/7937606/1_final_opinion_oel_1_4_dioxane_en.pdf.

11 *See, e.g.*, EPA (2023a) *Draft Supplement to the Risk Evaluation for 1,4-Dioxane* (hereinafter the 2023 Draft Supplement)*, CASRN 123-91-1*, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency (EPA), EPA Document # EPA-740-D-23-001, 484 pp., at 199, available at https://downloads.regulations.gov/EPA-HQ-OPPT-2016-0723-0103/content.pdf.

Tel: 202-249-6727

2. A description of the information the person believes does not comply with EPA or OMB guidelines, including specific citations to the information and to the EPA or OMB guidelines, if applicable.

The June 22, 2016, amendments to the Toxic Substances Control Act (TSCA) required EPA to initiate risk evaluations on ten chemical substances selected from the 2014 update of the Work Plan for Chemical Assessments and to publish this list of ten chemical substances within 180 days of enactment of the TSCA amendments.[12] On December 19, 2016, OPPT published the list of ten chemical substances, which included 1,4-DX.[13] Thereafter, OPPT released the draft risk evaluation for 1,4-DX with a request for comment on August 30, 2019.[14]

Prior to the close of the public comment period, OPPT held a peer review meeting from July 29-30, 2019, with its Science Advisory Committee on Chemicals (SACC).[15] The SACC reviewed the draft risk evaluation for 1,4-DX. During that meeting, a former EPA career employee and public commenter stated that "The staging of this SACC meeting does not reflect best management practices and is significantly in variance with the Agency's own guidance on the conduct of peer review."[16] The public commenter elaborated by

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12 TSCA § 6(b)(2)(A), 15 U.S.C. § 2605(b)(2)(A); EPA (2016) *Designation of Ten Chemical Substances for Initial Risk Evaluations Under the Toxic Substances Control Act*, Agency: Environmental Protection Agency (EPA), Action: Notice, FEDERAL REGISTER, Vol. 81, pp. 91927-91929, at 91927 (Dec. 19, 2016), available at https://www.govinfo.gov/content/pkg/FR-2016-12-19/pdf/2016-30468.pdf.

13 *Id*. at 91928.

14 EPA (2019a) *Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings*, Agency: Environmental Protection Agency (EPA), Action: Notice, FEDERAL REGISTER, Vol. 84, pp. 31315-31317, at 31315 (July 1, 2019), available at https://www.govinfo.gov/content/pkg/FR-2019-07-01/pdf/2019-14021.pdf.

15 EPA (2019b) *EPA Scientific Advisory Committee on Chemicals (SACC), Open Meeting, Toxic Substances Control Act, 1,4-Dioxane, Docket number: EPA-HQ-OPPT-2019-0238*, Holiday Inn Rosslyn at Key Bridge, 1900 Fort Myer Drive, Arlington, VA 22209 (July 29-30, 2019), 497 pp., available at https://downloads.regulations.gov/EPA-HQ-OPPT-2019-0238-0064/content.pdf.

16 *Id*. at 117.

stating that "the SACC will have concluded its review…before the public comment period closes…this approach is a case of either the arbitrary deadline for a decision is more important than the integrity of the information going into the decision, or this is a mechanism to discourage comments from the stakeholder community which desires to see a standardized risk evaluation process allowed, and followed, or both."[17]

On January 8, 2021, EPA announced the availability of the Final 1,4-DX RE.[18] EPA noted in that announcement that it was required, for those conditions of use (COU) for which unreasonable risks were identified, to "initiate regulatory action to address those risks through risk management measures enumerated in 15 U.S.C. 2605(a) [*i.e.*, TSCA Section 6(a)]."[19]

We note that OPPT chose to utilize a linear low-dose extrapolation when evaluating the potential carcinogenic risks from 1,4-DX in the Final 1,4-DX RE. This decision appears to be arbitrary and not in line with the best available science given the reasonably available information that informs the carcinogenic MOA for 1,4-DX, as discussed in Section 3 of this RFC, as well as the conclusions from other authoritative bodies that a threshold approach to cancer is appropriate for evaluating the potential carcinogenic risks from 1,4-DX.

Based on the foregoing, the IQA applies to the Final 1,4-DX RE because it is information that EPA disseminated to the public.[20] Further, the Final 1,4-DX RE is "influential" scientific information because OPPT is required under TSCA Section 6 to propose and promulgate a regulation that mitigates the unreasonable risks OPPT identified in the Final 1,4-DX RE. This regulation will have a "clear and substantial impact (i.e., potential change or effect) on important public policies or private sector decisions."[21] It is imperative, therefore, that EPA base its risk management actions on the best available science and weight of scientific evidence and not rely on an incomplete evaluation of the science as the

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17 *Id*.

18 EPA (2021a) *1,4-Dioxane; Final Toxic Substances Control Act (TSCA) Risk Evaluation; Notice of Availability*, Agency: Environmental Protection Agency (EPA), Action: Notice, FEDERAL REGISTER, Vol. 86, pp. 1495-1496 (Jan. 8, 2021), available at https://www.govinfo.gov/content/pkg/FR-2021-01-08/pdf/2021-00114.pdf.

19 *Id*. at 1496.

20 EPA (2002b), *supra* note 4, at 15.

21 *Id*. at 19.

basis for its decision making, as it did in the Final 1,4-DX RE. Moreover, TSCA requires EPA to meet this standard.[22]

3. An explanation of how the information does not comply with EPA or OMB guidelines and a recommendation of corrective action. EPA considers that the complainant has the burden of demonstrating that the information does not comply with EPA or OMB guidelines and that a particular corrective action would be appropriate.

Below, we discuss how OPPT's conclusion that data gaps in the carcinogenic MOA for 1,4-DX, led OPPT to apply a linear low-dose extrapolation, violates the scientific standards under TSCA. These standards do not supersede the requirements under the IQA or EPA's requirements for complying with the IQA. The scientific standards under TSCA are, however, consistent with the intent of the IQA for "Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the [EPA]."[23]

TSCA Section 26 includes the following requirements for "best available science" and "weight of scientific evidence":[24]

> (h) Scientific standards
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> In carrying out sections 2603, 2604, and 2605 of this title, to the extent that the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science …
>
> (i) Weight of scientific evidence
>
> The Administrator shall make decisions under sections 2603, 2604, and 2605 of this title based on the weight of the scientific evidence.

EPA interpreted TSCA Section 26(i) in the final "Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act" (the Final RE Rule) as:[25]

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22 TSCA at Section 26(h).

23 EPA (2002b), *supra* note 4, at 3-4.

24 TSCA § 26(h)-(i), 15 U.S.C. § 2625(h)-(i).

25 EPA (2017) *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* Agency: Environmental Protection Agency (EPA), Action: Final Rule, FEDERAL REGISTER, Vol. 82, pp. 33726-33753 at 33733 (July 20, 2017) (emphasis added), available at https://www.govinfo.gov/content/pkg/FR-2017-07-20/pdf/2017-14337.pdf.

> *Weight of scientific evidence means 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.

To help satisfy the scientific standards under TSCA Section 26 and the Final RE Rule in its risk evaluations, EPA released a document in May 2018 titled "Application of Systematic Review in TSCA Risk Evaluations" (2018 SR Document).[26] EPA used the 2018 SR Document for each of the "first 10" risk evaluations, including the risk evaluation on 1,4-DX. For example, the Final 1,4-DX RE states:[27]

> To meet these TSCA Section 26 science standards [*i.e.*, best available science and weight of the scientific evidence], EPA used the TSCA systematic review process described in the *Application of Systematic Review in TSCA Risk Evaluations* document.

Prior to completing the "first 10" risk evaluations, EPA requested the National Academies of Science, Engineering, and Medicine (NASEM) to review the 2018 SR Document. In February 2021, NASEM released its consensus study report (Consensus Study Report) on EPA's 2018 SR Document and concluded that it did not meet the criteria of "comprehensive, workable, objective, and transparent" and that "The OPPT approach to systematic review does not adequately meet the state-of-practice."[28]

NASEM recommended that "With regard to hazard assessment for human and ecological receptors, OPPT should step back from the approach that it has taken and consider

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26 EPA (2018) *Application of Systematic Review in TSCA Risk Evaluations*, EPA Document # 740-P1-8001, Office of Chemical Safety and Pollution Prevention (OCSPP) (May 2018), available at https://www.epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.

27 EPA (2020a), *supra* note 1, at 26.

28 NASEM (2021a) *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, Consensus Study Report, Highlights*, (Feb. 2021) at 4, available at https://www.nap.edu/resource/25952/TSCA%204-pager%20final.pdf.

components of the OHAT,[29] IRIS,[30] and Navigation Guide methods that could be incorporated directly and specifically into hazard assessment."[31] NASEM further stated that "OPPT also should evaluate how the existing OHAT, IRIS, and Navigation Guide methods could be modified for the other evidence streams."[32]

In response to the NASEM review, EPA revised its systematic review method. On December 20, 2021, EPA released the 2021 Draft Protocol for public comment.[33] EPA acknowledged in the 2021 Draft Protocol that:[34]

> Previously [in the 2018 SR Document], EPA did not have a complete clear and documented TSCA systematic review (SR) Protocol. EPA is addressing this lack of a priori protocol by releasing [the 2021 Draft Protocol].

EPA further stated that the:[35]

> [2021 Draft Protocol] is significantly different [from the 2018 SR Document] in that it includes descrition [sic] of the Evidence

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29 OHAT is the abbreviation for the U.S. National Toxicology Program's Office of Health Assessment and Translation (OHAT).

30 IRIS is the abbreviation for EPA's Integrated Risk Information System (IRIS).

31 NASEM (2021a), *supra* note 28.

32 *Id*.

33 EPA (2021b) *Science Advisory Committee on Chemicals (SACC); Notice of Public Meeting and Request for Comments on Draft Toxic Substances Control Act (TSCA) Systematic Review Protocol* Agency: Environmental Protection Agency (EPA), Action: Notice, FEDERAL REGISTER, Vol. 86, pp. 71891-71893 (Dec. 20, 2021), available at https://www.govinfo.gov/content/pkg/FR-2021-12-20/pdf/2021-27437.pdf.

34 EPA (2021c) *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0, A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies* (2021 Draft Protocol), OCSPP, EPA Document # EPA-D-20-031 (Dec. 2021) at 25, available at https://www.epa.gov/system/files/documents/2021-12/draft-systematic-review-protocol-supporting-tsca-risk-evaluations-for-chemical-substances_0.pdf.

35 *Id*. at 27.

> Integration process…, which was not previously included in the [2018 SR Document].

We recognize that the scientific methods used to inform systematic review are not static and that updates will be required as the science evolves. In this instance, however, many of the documents cited as supporting information for updating the 2021 Draft Protocol (*e.g.*, OHAT, 2015)[36] were available prior to EPA issuing the 2018 SR Document. Rather than utilizing these available documents, OPPT developed the 2018 SR Document *de novo*. In other words, OPPT chose to develop its own methodology in 2018 rather than incorporating and adapting existing methodologies that represented the best available science at the time. NASEM recognized this and concluded that:[37]

> In the committee's judgment, the specific and general problems in TSCA risk evaluations are partially due to the decision to develop a largely de novo approach, rather than starting with the foundation offered by approaches that were extant in 2016.

These problems were pervasive in the "first 10" risk evaluations. For example, OPPT provided NASEM with example risk evaluations to assess during its review. One of the example risk evaluations was the draft risk evaluation on trichloroethylene (TCE), which OPPT described as representing the "best example of integration,"[38] among the available risk evaluations. NASEM disagreed and concluded that:[39]

> [T]he hazard assessment within the TSCA TCE risk evaluation was of critically low quality, meaning that the review had "more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies."

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36 OHAT (2015), *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration*, OHAT, Division of the National Toxicology Program (NTP), National Institute of Environmental Health Sciences (Jan. 9, 2015), available at https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf.

37 NASEM (2021b), *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations*, Washington, D.C.: The National Academies Press, at 7, available at https://doi.org/10.17226/2595283.

38 *Id*. at 2.

39 *Id*. at 52 (citation omitted).

Though NASEM did not evaluate the risk evaluation for 1,4-DX, OPPT's hazard assessment in the Final 1,4-DX RE was also of critically low quality and inconsistent with the scientific standards of TSCA Section 26. OPPT was aware of the deficiencies with its 2018 SR Document, prior to the NASEM review. For example, during the SACC peer review meeting on the draft risk evaluation for 1,4-DX, a public commenter identified various issues with OPPT's systematic review, including:[40]

> The first critical piece of missing information is creating a protocol which is used to review all the evidence and outline the process for conducting the review. *This helps minimize bias and ensure transparency in the decision-making process*. It's also required by law to have a preestablished protocol, and there's not one for 1,4-Dioxane or the other TSCA chemicals.

OPPT's systematic review of the reasonably available information on 1,4-DX did not meet the requirements of best available science and weight of scientific evidence, as required under TSCA Sections 26(h) and 26(i), respectively, and the implementing TSCA regulations. Despite this, OPPT failed to address these weaknesses and utilized again its previous conclusions from the Final 1,4-DX RE to inform its unreasonable risk determinations in the 2023 Draft Supplement.

OPPT stated in the Final 1,4-DX RE that it "evaluated proposed modes of action (MOAs) for 1,4-dioxane carcinogenicity using the MOA framework proposed in EPA's [2005] *Guidelines for Carcinogenic Risk Assessment*" (hereinafter the 2005 Cancer Guidelines).[41] OPPT further stated:[42]

> [It] does not have sufficient information to determine whether carcinogenic effects of 1,4-dioxane at each tumor site are mediated by the parent compound, metabolites, or both. The most well-developed MOAs for 1,4-dioxane carcinogenicity focus on the MOA for liver tumors. Therefore, this MOA analysis focuses on plausible MOAs of 1,4-dioxane liver carcinogenicity.

The 2005 Cancer Guidelines state:[43]

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40 EPA (2019b), *supra* note 15, at 125-126 (emphasis added).

41 EPA (2020a), *supra* note 1, at 499.

42 *Id*.

43 EPA (2005) *Guidelines for Carcinogen Risk Assessment*, Risk Assessment Forum, U.S. Environmental Protection Agency (EPA), EPA/630/P-03/001B, 166 pp., at 1-10, available at https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf.

> The term "*mode of action*" is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A "*key event*" is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element. Mode of action is contrasted with "*mechanism of action*," which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action.

EPA's distinction between "mode of action" and "mechanism of action" indicates that the 2005 Cancer Guidelines allow for the accommodation of data gaps, a premise that OPPT dismissed in its evaluation of the potential carcinogenic MOAs for 1,4-DX yet one that other authoritative bodies recognize. For example, the ECHA RAC concluded that "although some uncertainty on the mode of action remains, the carcinogenicity of 1,4-dioxane is considered to be related to a non-genotoxic mechanism, involving saturation of metabolic capacity, irritation at high exposure levels and formation of liver tumours by regenerative proliferation."[44]

OPPT identified four potential MOAs for liver carcinogenicity, including metabolic saturation and cytotoxicity followed by proliferative regeneration (MOA #1), proliferation in the absence of cytotoxicity (MOA #2), mutagenic and other genotoxic mechanisms (MOA #3), and CAR/PXR-mediated effects (MOA #4). OPPT evaluated MOA #1 according to the 2005 Cancer Guidelines framework analysis yet dismissed MOAs #2-#4 after concluding without a review of reasonably available information, as required under TSCA Section 26(k), that there was insufficient information for a complete evaluation.[45] Herein, we provide feedback on OPPT's framework analysis based on its evaluation provided in Appendix J of the Final 1,4-DX RE, which was not updated as part of OPPT's release of the 2023 Draft Supplement, despite the known weakness of the systematic review used in the Final 1,4-DX RE and the assessments of other competent authorities.

MOA #1: Metabolic saturation, cytotoxicity and proliferative regeneration

OPPT described MOA #1 as follows: "In this proposed MOA, metabolic saturation leads to accumulation of the parent compound 1,4-dioxane. Accumulated 1,4-dioxane then causes cytotoxicity by an undetermined mechanism. Cytotoxicity is followed by regenerative proliferation, leading to liver tumors."[46]

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44 ECHA (2022a), *supra* note 10, at 7.

45 EPA (2020a), *supra* note 1, at 499-500.

46 *Id*. at 500.

OPPT's statement about an "undetermined mechanism" fails to consider information presented to OPPT, which described new key events (KE) in the carcinogenic MOA for 1,4-DX, including a direct mitogenic response, as discussed under MOA #2.

Metabolic saturation & 1,4-DX accumulation in the blood.

OPPT's framework analysis of MOA #1 began with evaluating the toxicokinetics of 1,4-DX, which it acknowledged as indicating "that while metabolism of 1,4-dioxane follows first-order kinetics at lower doses, higher oral doses exhibit nonlinear Michaelis-Menten kinetics [citations omitted]."[47] OPPT then dismissed metabolic saturation as a KE for MOA #1, based on a 13-week inhalation study (*i.e.*, Kasai *et al*., 2008) that reported first-order kinetics in rats exposed to 1,4-DX concentrations between 400 and 3200 ppm.[48] Kasai *et al*. (2008) measured blood 1,4-DX concentrations in rats "1 h after termination of day 3 exposure in wk 12 of the 13-wk exposure period."[49]

Kasai *et al*. (2008) interpreted these data as an indication of "enhanced metabolism by the possible induction of P450 enzymes including CYP2E1."[50] Though this is one plausible interpretation of these data and one that OPPT accepted, Lafranconi *et al*. (2023) noted that "there was no time-course sampling to enable detection of a possible threshold response."[51] Regardless, CYP2E1 activation and oxidative stress are new KEs in the MOA for 1,4-DX, as proposed by Lafranconi *et al*. (2023), that precede cellular damage.[52] In comparison, OPPT's interpretation of these data for MOA #1 led it to conclude that "metabolic

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47 *Id*. at 506.

48 *Id*.

47 Kasai *et al*. (2008) *Thirteen-Week Inhalation Toxicity of 1,4-Dioxane in Rats*, INHALATION TOXICOLOGY, Vol. 20, pp. 961-971, at 963, available at https://doi.org/10.1080/08958370802105397.

50 *Id*. at 969.

49 Lafranconi *et al*. (2023) *An Integrated Assessment of the 1,4-Dioxane Cancer Mode of Action and Threshold Response in Rodents*, REGULATORY TOXICOLOGY AND PHARMACOLOGY, Vol. 142, 17 pp., at 10, available at https://doi.org/10.1016/j.yrtph.2023.105428.

52 *Id*. at 12.

saturation may not be a necessary key event for liver tumor formation" and that "liver toxicity due to metabolites of 1,4-dioxane cannot be ruled out."[53]

OPPT concluded that there was insufficient evidence (*i.e.*, a data gap) for MOA #1 and the linkage between metabolic saturation/1,4-DX accumulation in the blood and hepatocellular toxicity. OPPT holds this view despite the fact that the MOA proposed by Lafranconi *et al*. (2023) provides sufficient evidence to inform this linkage *via* direct mitogenesis, CYP2E1 activation, oxidative stress, and then cellular damage.[54]

Sustained activation of CYP2E1 is recognized as an MIE that leads to liver cancer and has a well-developed adverse outcome pathway (AOP).[55] Further, the Organisation for Economic Co-operation and Development (OECD) endorsed this AOP (*i.e.*, AOP: 220).[56] EPA participated in the joint OECD effort that led to the development of the AOP-Wiki, along with the OECD's handbook supplement to its guidance document on developing and assessing AOPs.[57,58] Therefore, OPPT's unjustified dismissal of this AOP is inconsistent with the spirit and intent of the OECD's multilateral agreement on the mutual acceptance of data, which is aimed at harmonizing the development of information for regulatory assessments and ensuring confidence in that information, regardless of where or from whom it is generated.[59] Rather, OPPT seems to simply select its preferred conclusion (non-

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53 EPA (2020a), *supra* note1, at 506.

54 Lafranconi *et al*. (2023), *supra* note 51, at 12.

55 Webster *et al*. (2023) *Cyp2E1 Activation Leading to Liver Cancer*, AOP: 220 (last modified on Apr. 29, 2023), AOP Wiki, available at https://aopwiki.org/aops/220#prototypical-stressors.

56 *Id*.

57 AOP-Wiki (2023) *About the Adverse Outcome Pathway Wiki (AOP-Wiki)*, available at https://aopwiki.org/info_pages/3.

58 OECD (2022) *Users' Handbook Supplement to the Guidance Document for Developing and Assessing AOPs*, Series on Testing & Assessment No. 233, Series on Adverse Outcome Pathways No. 1, Organisation for Economic Co-operation and Development (OECD), ENV/JM/MONO(2016)12, 60 pp., available at https://one.oecd.org/document/ENV/JM/MONO(2016)12/en/pdf.

59 *See generally* OECD (2023) Mutual Acceptance of Data (MAD), Organisation for Economic Co-operation and Development (OECD), available at https://www.oecd.org/chemicalsafety/testing/MAD-briefing-notes-EHS.pdf.

threshold carcinogenicity) and perfunctorily dismiss information that repudiates that conclusion.

Hepatocellular toxicity.

OPPT further stated that "While evidence of cytotoxicity was also observed in some 2-year cancer bioassays [citations omitted], it was not consistently seen as a precursor to carcinogenic lesions in all studies. For example, liver tumors in female mice were observed in the absence of hepatocellular toxicity [citing Kano *et al*., 2009]."[60] This suggests that cytotoxicity is not driving the tumor response. Further, OPPT is relying on a controversial study with findings that are inconsistent with the weight of scientific evidence from other studies in rats and mice. OPPT is the only regulatory body in the world to rely upon the Kano *et al*. (2009) study. This study was performed by the Japan Bioassay Research Center (JBRC), yet Japan does not base its drinking water standard for 1,4-DX on the Kano *et al*. (2009) study and instead appears to rely on the World Health Organization's (WHO) guideline value of 0.05 mg/L.[61,62]

Lafranconi *et al*. (2023) reviewed the issues with Kano *et al*. (2009), including:[63]

1) The Kano et al. (2009) study in Crj:BDF1 female mouse demonstrated a near maximum liver tumor response (e.g., 70%) at the lowest dosage tested (66 mg/kg/d) that increased modestly to 92% at the highest dosage (964 mg/kg/d). In contrast, the 1978 NCI study in B6C3F1 female mice demonstrated a more abrupt increase in treatment-related liver tumors, where tumor incidence increased from 44% at 380 mg/kg/d to 95% at 860 mg/kg/d.

2) The 13-week mouse drinking water study (Kano et al., 2008) reported non-neoplastic liver pathology that was

60 EPA (2020a), *supra* note 1, at 506.

59 MHLW (2015) *Drinking Water Quality Standards in Japan (April 2015~)*, Japanese Ministry of Health, Labour and Welfare (MHLW), available at https://www.mhlw.go.jp/english/policy/health/water_supply/dl/4a.pdf.

62 WHO (2005) *1,4-Dioxane in Drinking Water, Background Document for Development of WHO Guidelines for Drinking-water Quality*, World Health Organization (WHO), WHO/SDE/WSH/05.08/120, 20 pp., at 9, available at https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/dioxane-bd.pdf.

63 Lafranconi *et al*. (2023), *supra* note 51, at 5.

inexplicably not reported in the 2-year study. In addition, similar non-neoplastic findings were also observed in the re-read of the liver slides from the NCI study (Dourson et al., 2014) indicating that the reporting of pre-neoplastic findings from the chronic study by Kano was incomplete.

3) The diagnostic criteria used in the original JRBC report (JBRC, 1990) and associated conference proceeding (Yamazaki et al., 1994) changed in the subsequent peer-reviewed publication of the same study (Kano et al., 2009).

The Kano *et al*. (2009) study appears to be an outlier in the available chronic oral toxicity data on 1,4-DX in mice and rats. The underlying basis for the 70% tumor response in female Crj:BDF1 mice observed at a dose nearly six-fold lower than the dose causing a 44% increase in tumor response in female B6C3F1 mice is unclear and OPPT provides no explanation. This could represent a unique susceptibility of female Crj:BDF1 mice to the effects from 1,4-DX. Alternatively, it may reflect an issue with the subsequent change in classification of tumors, as reported by Kano *et al*. (2009). Health Canada (2021) questioned the results of Kano *et al*. (2009), noting the "large degree of uncertainty [that] exists regarding the liver tumour occurrence in female mice [citations omitted] at ≥66 mg/kg bw per day," that "liver tumours were generally reported at higher doses (LOAELs of 274-1599 mg/kg bw per day) in the other chronic studies…[, and] [t]he absence of non-cancer histopathological changes and the concomitant increase in liver enzymes in the JBRC studies despite the presence of both endpoints in the sub-chronic studies from the same group…"[64]

Despite the well-documented issues regarding the quality of Kano *et al*. (2009), OPPT assigned a data quality rating of "High" using the 2018 SR Document, which defined this level of confidence as "No notable deficiencies or concerns are identified and the data therefore could be used in the assessment with a high degree of confidence."[65] This is an important consideration given that OPPT stated it "is not using, and will not again use, the 2018 systematic review approach document…,"[66] based on the feedback it received from NASEM on the 2018 SR Document. As indicated previously, NASEM concluded that "The

64 Health Canada (2021), *supra* note 9, at 29-30.

65 EPA (2018), *supra* note 26, at 34.

66 EPA (2023b) *Draft Protocol for Systematic Review in TSCA Risk Evaluations*, Assessing and Managing Chemicals under TSCA, U.S. Environmental Protection Agency (EPA), available at https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/draft-protocol-systematic-review-tsca-risk-evaluations.

OPPT approach to systematic review does not adequately meet the state-of-practice,"[67] and, as noted, OPPT was aware of the deficiencies with its 2018 SR Document, prior to the NASEM review, including its failure to have a "preestablished protocol," as required by the implementing regulations under TSCA. OPPT only conceded, following NASEM's feedback, that it "did not have a complete clear and documented TSCA systematic review (SR) Protocol…[and stated that it]…is addressing this lack of *a priori* protocol by releasing [the 2021 Draft Protocol]."[68] OPPT did not, however, do anything to remedy this failure in the Final 1,4-DX RE nor in subsequent evaluations it performed on 1,4-DX, including the 2023 Draft Supplement.

Regenerative cell proliferation.

OPPT continued its evaluation of MOA #1 by considering regenerative cell proliferation. OPPT stated that "Evidence in rat bioassays supports the occurrence of cell proliferation prior to liver tumor formation [citations omitted]."[69] OPPT then expressed concerns over several areas it identified as unknowns, including:[70]

1. "[T]he dose-response relationship for induction of cell proliferation has not been characterized";

2. "[I]t is unknown if there is a dose-response relationship between cell proliferation and liver tumors in the 2-year cancer bioassays in rat and mouse studies";

3. "It is unknown whether the increased rates of DNA synthesis observed in response to 1,4-dioxane exposure represent a true increase in cellular proliferation rates or if this increase is a cellular response to DNA damage and the repair of those lesions"; and

4. "It is also unknown whether observed cell proliferation is a direct response to cytotoxicity and whether it is caused by 1,4-dioxane or a metabolite."

The unknowns identified by OPPT were addressed by Lafranconi *et al*. (2023). For example, unknowns #s 1, 3, and 4 above were informed by the experiments conducted by

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67 NASEM (2021a), *supra* note 28.

68 EPA (2021c), *supra* note 34, at 25.

69 EPA (2020a), *supra* note1, at 507.

70 *Id*.

Lafranconi *et al*. (2021)[71] and Chappell *et al*. (2021)[72] and summarized by Lafranconi *et al*. (2023) as follows:[73]

> Lafranconi et al. (2021) evaluated both the dose-response and time course of hepatic events of female B6D2F1 mice treated with 20, 40, 200, 600, 2000 or 6000 ppm 1,4-DX in drinking water for 7, 28 or 90 days. Liver weight increases after 90 days of exposure were accompanied by evidence of increased pan-lobular hepatocellular proliferation as determined by increased BrdU incorporation. Other than limited evidence of single-cell necrosis typical of apoptosis, there was no histological or biochemical evidence of cytotoxicity at any of the exposures used in this study. There was evidence of changes in genomic signaling only at 2000 ppm (337–391 mg/kg/d) and 6000 ppm (895–1063 mg/kg/d) from whole transcriptome analyses consistent with mitotic events (Chappell et al., 2021).

Unknown #2 was also discussed by Lafranconi *et al*. (2023) and is discussed under MOA #2, given its relevance to that MOA. Unknown #2 was also informed by the slide re-review performed by McConnell (2013)[74] on the 1978 bioassay performed by the National Cancer Institute (NCI). McConnell (2013) concluded that the "slide review supports the view that there are clearly identifiable dose-related non-neoplastic changes in the liver of mice exposed to 1,4–dioxane. The most clear examples of a dose-related effect are the hypertrophic response of hepatocytes, followed by necrosis/inflammation and hyperplastic hepatocellular foci."[75]

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69 Lafranconi *et al*. (2021) *A 90-Day Drinking Water Study in Mice to Characterize Early Events in the Cancer Mode of Action of 1,4-Dioxane*, REGULATORY TOXICOLOGY AND PHARMACOLOGY, Vol. 119, 8 pp., available at https://doi.org/10.1016/j.yrtph.2020.104819.

70 Chappell *et al*. (2021) *Transcriptomic Analyses of Livers from Mice Exposed to 1,4-Dioxane for up to 90 Days to Assess Potential Mode(s) of Action Underlying Liver Tumor Development*, CURRENT RESEARCH IN TOXICOLOGY, Vol. 2, pp. 30-41, available at https://doi.org/10.1016/j.crtox.2021.01.003.

73 Lafranconi *et al*. (2023), *supra* note 51, at 13.

74 McConnell (2013) *Report on the review of liver slides from the National Cancer Institute's bioassay of 1,4-dioxane for possible carcinogenicity conducted in 1978*, Technical Report, 17 pp., available at http://allianceforrisk.org/wp-content/uploads/2015/10/14-Dioxane-Pathology-report-Final-18-march-2013.pdf.

75 *Id*. at 4.

Hyperplasia.

OPPT stated that "Hepatocyte hyperplasia was reported in rats and mice following 1,4-dioxane exposure in several studies [citations omitted]; however, the hyperplasia originally reported by Yamazaki et al. and JBRC was subsequently reexamined histopathologically and changed to hepatocellular adenoma and altered hepatocellular foci Kano et al. (2009)."[76] OPPT further stated that "it considered previously unavailable incidence data from Kociba et al. 1974) [*sic*]. This new data suggests there may be a dose-response relationship between 1,4-dioxane and bile duct epithelial hyperplasia, but [they] did not show a dose-response relationship between 1,4-dioxane and hepatocellular hyperplasia or demonstrate hyperplasia precedes tumor formation."[77]

As noted previously, there are issues with the Kano *et al*. (2009) study in mice that raise concerns about OPPT's reliance on these data, including that other authoritative regulatory agencies reviewed these same data and did not rely on them.[78] The data from Kociba *et al*. (1974) in rats support the MOA developed by Lafranconi *et al*. (2023), which "suggest cytotoxicity is a late developing KE in the cancer MOA of 1,4-DX."[79] OPPT's summary of the histopathology incidence data from Kociba *et al*. (1974) supports this given the dose-dependent increase in hepatocellular vacuolar degeneration and necrosis observed in male and female rats.[80]

Preneoplastic foci development and clonal expansion.

OPPT stated that "There is limited evidence of foci development and clonal expansion following 1,4-dioxane exposure in a tumor promotion study. Following initiation with diethylnitrosoamine, a high dose (1000 mg/kg/day by oral gavage) of 1,4-dioxane administered to rats 5 times a week for 6 weeks was associated with a significant increase in the number and volume of foci Lundberg et al. (1987)."[81]

The findings cited by OPPT support the proposed MOA by Lafranconi *et al*. (2023) that 1,4-DX acts as a direct mitogen.[82] Moreover, OPPT's statement that "foci of altered

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76 EPA (2020a), *supra* note 1, at 507.

77 *Id*.

78 *See, e.g.*, Health Canada (2021), *supra* note 9, at 29-30.

79 Lafranconi *et al*. (2023), *supra* note 5190, at 13.

80 EPA (2020a), *supra* note1, at 523-524.

81 *Id*. at 507.

hepatocytes may progress to hepatocarcinogenesis with or without an intermediary neoplastic nodular stage (that may lag for weeks or months after foci development and before progression to hepatocarcinomas)"[83] is misleading.

Maronpot *et al*. (1986) stated that terms such as "*foci of cellular alteration*, *hepatocellular adenoma*, and *hepatocellular carcinoma* are believed to represent a spectrum of changes that comprise the *natural history of neoplasia*. Each of these terms reflects our knowledge regarding the autonomy of the lesion and its biological potential at the time of sampling [emphasis in original]."[84] Further, the overview to this article included the following statements about "neoplastic nodules":[85]

> [T]he imposition of a new, misunderstood term, *neoplastic nodule* which essentially left the less decisive diagnostic pathologist off the hook. If not convinced, call it neoplastic nodule, rather than hyperplastic nodule, and the diagnosis would not likely be challenged by reviewing panels. This allowance for lack of confidence and self-discipline has permitted some potentially useful drugs and chemicals to be unfairly categorized as carcinogens, sometimes to be reassigned by a more discerning group of pathologists at a later review.

OPPT did not cite to Maronpot *et al*. (1986) as part of its argumentation; rather, it cited to articles that were published many years before the U.S. National Toxicology Program abandoned this diagnostic terminology for hepatoproliferative lesions in rats.[86]

Tumor formation.

OPPT stated that "There is clear and consistent evidence of a significant increase in liver tumor formation (including adenomas and carcinomas) in rats and mice exposed to 1,4-

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82 *Id*.

83 *Id*. at 508.

84 Maronpot *et al*. (1986) *National Toxicology Program Nomenclature for Hepatoproliferative Lesions in Rats*, TOXICOLOGIC PATHOLOGY, Vol. 14, pp. 263-273, at 272, available at https://doi.org/10.1177/019262338601400217.

85 *Id*. at 263.

86 EPA (2020a), *supra* note 1, at 507-508.

dioxane through drinking water and in rats exposed through inhalation [citations omitted]."[87]

We concur with OPPT's conclusions on this endpoint, although we disagree with OPPT on the doses at which tumors may occur.

MOA #2: Cell proliferation in the absence of cytotoxicity [i.e., mitogenesis].

OPPT summarized MOA #2 as follows:[88]

> It is possible that 1,4-dioxane or a metabolite leads to cell proliferation in the absence of cytotoxicity. This potential MOA has not been articulated in the peer-reviewed literature and there is insufficient information to determine the specific key events through which 1,4-dioxane or its metabolites may lead to proliferation.

During the EPA's SACC review meeting on the draft risk evaluation for 1,4-DX on July 29, 2019, public commenters presented on a 90-day drinking water study in mice aimed at characterizing early events in the carcinogenic MOA for 1,4-DX.[89] The presented information was subsequently published in the peer-reviewed scientific literature.[90,91,92]

Lafranconi *et al*. (2021) determined through experimentation that their results "provide further evidence for the metabolic saturation of clearance pathways as a KE leading to accumulation of systemic 1,4-DX."[93] The study authors also noted "a time- and dose-dependent threshold for this saturation and the development of the subsequent KE [*i.e.*, a direct mitogenic response]." The study authors found that "the direct mitogenic stimulation observed in this study, approximately a five-fold increase in liver proliferation (labeling index) in the 6000 ppm exposure group after 90 days, occurs prior to the development of

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87 *Id*. at 508.

88 *Id*. at 499.

89 EPA (2019b), *supra* note 15, at 111-115 and 156-165.

90 Lafranconi *et al*. (2023), *supra* note 51.

91 Lafranconi *et al*. (2021), *supra* note 71.

92 Chappell *et al*. (2021), *supra* note 72.

93 Lafranconi *et al*. (2021), *supra* note 71, at 5.

cytotoxicity and regenerative repair that is a cornerstone of the regenerative hyperplasia MOA."[94]

Lafranconi *et al*. (2023) concluded that "the current compilation of data sets from mice and rats demonstrate that 1,4-DX causes an early and direct mitogenic response absent cytotoxicity; this reduced the need for cytotoxicity-driven regenerative repair in the MOA sequence."[95] These authors further concluded that "The evidence of cytotoxicity from shorter-term studies is less compelling and suggest cytotoxicity is a late developing KE in the cancer MOA of 1,4-DX."[96]

OPPT's dismissal of the Lafranconi *et al*. (2021) data "as effects not specific to carcinogenicity" conflicts with the 2005 Cancer Guidelines, which acknowledge precursor responses, such as mitogenic effects, that are integral to the carcinogenic process,[97] and the MOA as proposed by Lafranconi *et al*. (2021, 2023).[98,99]

The potential MOA for cellular proliferation in the absence of cytotoxicity was published in the peer-reviewed literature, albeit after OPPT published the Final 1,4-DX RE. The experimental data and evidence integration that informed this MOA and earlier KEs, however, were communicated to OPPT during the SACC peer review meeting on the draft risk evaluation for 1,4-DX.[100] OPPT does not adequately address why it continues to reject the conclusions from the Lafranconi *et al*. (2021, 2023) and Chappell *et al*. (2021) publications.

MOA #3: Mutagenicity and other forms of genotoxicity.

OPPT summarized MOA #3 as follows:[101]

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94 *Id*. at 6.

95 Lafranconi *et al*. (2023), *supra* note 51, at 13.

96 *Id*.

97 EPA (2005), *supra* note 43, at A-9.

98 Lafranconi *et al*. (2021), *supra* note 71, at 6.

99 Lafranconi *et al*. (2023), *supra* note 51, at 12.

100 EPA (2019b), *supra* note 15, at 111-115.

101 EPA (2020a), *supra* note 1, at 500.

> [T]here is insufficient data to determine whether 1,4-dioxane is mutagenic or induces cancer through a mutagenic MOA. In the absence of other information about MOA, EPA often takes the health protective approach of assuming a linear no-threshold risk model consistent with a mutagenic MOA.

We disagree that application of a linear low-dose approach is health protective if the science does not support the approach. OPPT appears to be using a non-risk factor (its preference for a non-threshold approach) as a means of justifying its risk determination, rather than revising the Final 1,4-DX RE by incorporating reasonably available information into this document to ensure its subsequent use (*e.g.*, the 2023 Draft Supplement) reflects the best available science and weight of scientific evidence for the carcinogenic MOA for 1,4-DX.

OPPT first began evaluating 1,4-DX under TSCA in 2014 as a work plan chemical risk assessment.[102] OPPT subsequently published the *TSCA Work Plan Chemical Problem Formulation and Initial Assessment for 1,4-Dioxane* (hereinafter 1,4-DX Initial Assessment) in 2015.[103] As part of its hazard assessment at that time, OPPT concluded, based on a 2013 assessment conducted by EPA's Office of Research and Development (ORD),[104] that 1,4-DX "is nongenotoxic or weakly genotoxic."[105] In comparison, OPPT concluded in the Final 1,4-DX RE that "there is some evidence for genotoxicity in vivo at high doses, but there is insufficient evidence to conclude that 1,4-dioxane is mutagenic or induces cancer through a mutagenic mode of action."[106] OPPT reviewed two *in vivo* gene

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100 EPA (2014) *TSCA Work Plan for Chemical Assessments: 2014 Update*, Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency (EPA), 36 pp., at 13, available at https://www.epa.gov/sites/default/files/2015-01/documents/tsca_work_plan_chemicals_2014_update-final.pdf.

101 EPA (2015) *TSCA Work Plan Chemical Problem Formulation and Initial Assessment*, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency (EPA), EPA Document # 740-R1-5003, available at https://www.epa.gov/sites/default/files/2017-06/documents/14_dioxane_problem_formulation_and_intial_assessment.pdf.

104 EPA (2013) *Toxicological Review of 1,4-Dioxane (with inhalation update) (CAS No. 123-91-1) In Support of Summary Information on the Integrated Risk Information System (IRIS)*, U.S. Environmental Protection Agency (EPA), EPA/635/R-11/003F, 419 pp., at 73, available at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf.

105 EPA (2015), *supra* note 103, at 29.

106 EPA (2020a), *supra* note 1, at 170.

mutation assays that were published after the 2013 ORD assessment and OPPT's 2015 1,4-DX Initial Assessment. OPPT summarized these studies, noting that one study (*i.e.*, Itoh and Hittori, 2019) was negative that assessed gene mutations with the *Pig-a* assay, whereas a second study (Gi *et al*., 2018) that assessed gene mutations in *gpt* delta transgenic F344 rats was positive.

OPPT agreed with the conclusions of the authors of both studies, including those of Gi *et al*. (2018) that "no genotoxic or mutagenic effect [was identified] in transgenic animals in the lowest dose group (18.7 mg/kg/day)."[107] Further, the recent evaluation from Health Canada (2021) concluded, after evaluating Gi *et al* (2018), that "1,4-dioxane acts through a non-genotoxic MOA."[108]

Lafranconi *et al*. (2023) performed a critical review of Gi *et al*. (2018) and noted that these authors "suggested that the increased expression of methylguanine methyltransferase (MGMT) repair protein at the high dose of 5000 ppm is the key line of evidence for a mutagenic MOA."[109] Lafranconi *et al*. (2023) further noted that "MGMT prevents G-to-A mutations, and those transitions were not increased in the Gi *et al*. (2018) study. Instead, [Gi et al., 2018] found mutations at the A:T base pair, specifically A-to-G and A-to-T mutations, predominating as a result of 1,4-DX treatment (Gi et al., 2018)."[110] This finding is consistent with other more recent findings that identified a possible role of oxidative stress in the formation of DNA adducts of 1,4-DX treated animals. For example, Totsuka *et al*. (2021)[111] reviewed their previous research[112] on 1,4-DX where they performed an untargeted DNA adductome study on frozen liver samples from 1,4-DX treated *gpt* delta rats (*i.e.*, samples from Gi *et al*., 2018). The authors identified three candidate adducts that were characteristic of 1,4-DX treatment, including two that contained thymine or

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107 *Id*.

108 Health Canada (2021), *supra* note 9, at 40.

109 Lafranconi *et al*. (2023), *supra* note 51, at 9.

110 *Id*.

109 Totsuka *et al*. (2021) *New Horizons of DNA Adductome for Exploring Environmental Causes of Cancer*, CANCER SCIENCE, Vol. 112, pp. 7-15, at 10, available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/cas.14666.

110 Totsuka *et al*. (2020) *Comprehensive Analysis of DNA Adducts (DNA Adductome Analysis) in the Liver of Rats Treated with 1,4-Dioxane*, PROCEEDINGS OF THE JAPAN ACADEMY. SERIES B, PHYSICAL AND BIOLOGICAL SCIENCES, Vol. 96, pp. 180-187, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7248212/pdf/pjab-96-180.pdf.

cytidine/uracil and a third identified as 8-hydroxy-2'-deoxyguanosine (8-oxo-dG). The authors interpreted their finding as suggesting that "oxidative stress responses could account for the increased frequency of mutations resulting from 1,4-dioxane treatment."[113] It is noteworthy that Totsuka *et al*. (2020) discussed the absence of an increase in 8-oxo-dG in their previous evaluation of livers of *gpt* delta rats, as reported by Gi *et al*. (2018). Totsuka *et al*. (2020) stated that the discrepancy between their work and previous evaluation for 8-oxo-dG performed by Gi *et al*. (2018) was unclear and that "differences in sample preparation and detection methods may have influenced the results." Further, the research of Chen *et al*. (2022) showed that lipid peroxidation and oxidative stress were likely the operational mechanisms through which 1,4-DX causes liver carcinogenicity in mice.[114]

The above data support that the carcinogenic MOA for 1,4-DX involves a threshold with mutagenicity occurring as a secondary effect to oxidative stress, yet OPPT dismisses this evidence with a perfunctory statement that there is still "insufficient information" to reach this conclusion. In light of the aforementioned, it is unclear how and why OPPT reached that conclusion.

MOA #4: CAR/PXR mediated effects.

OPPT summarized MOA #3 as follows:

> [T]he key events in the MOA linking 1,4-dioxane to CAR-mediated carcinogenicity have not been clearly articulated in the literature, and 1,4-dioxane has not been identified as a CAR agonist. One 16-week drinking water exposure study in transgenic rats evaluated a panel of CYP enzymes that are induced by nuclear receptors CAR, PXR, PPARα, or AhR and found no changes in mRNA expression of these CYPs in rat livers following 1,4-dioxane exposure Gi et al. (2018). No studies have evaluated this mechanism in the presence of tumor formation. EPA concluded that there is insufficient chemical-specific data to meaningfully evaluate this proposed MOA.

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113 Totsuka *et al*. (2021), *supra* note 111, at 10.

114 Chen *et al*. (2022) *Oxidative Stress and Genotoxicity in 1,4-Dioxane Liver Toxicity as Evidenced in a Mouse Model of Glutathione Deficiency*, SCIENCE OF THE TOTAL ENVIRONMENT, Vol. 806, 150703, available at https://doi.org/10.1016/j.scitotenv.2021.150703.

Lafranconi *et al*. (2023) evaluated the potential role of nuclear receptors (NR) (*i.e.*, CAR/PXR, AhR, and PPARα) in the carcinogenic MOA for 1,4-DX.[115] These authors concluded that the reasonable available information "are not indicative of a NR-mediated rodent hepatocarcinogen but clearly indicate the dose- and temporal-threshold nature of hepatocellular proliferation, along with shifts in metabolism."[116] Chappell *et al*. (2021)[117] determined that 1,4-DX treatment in mice did not increase CYP-encoding genes that are common indicators of CAR, AhR, or PPARα activation. The authors did note a significant upregulation of the PXR-related *Cyp3a11* (human homolog *CYP3A4*) in mice treated with 6000 ppm (the highest dose), but this response was only observed at the 90-day timepoint. The dose- and temporal-nature of this finding lends further support that nuclear receptor activation is unlikely to play a role in the carcinogenic MOA of 1,4-DX.

4. An explanation of how the alleged error affects or how a correction would benefit the requestor.

The above discrepancies with OPPT's framework analysis of the carcinogenic MOA of 1,4-DX are problematic. OPPT admittedly used a flawed systematic review method when evaluating studies that formed the basis for its evaluation. Further, OPPT does not explain if or when it will remedy this failure and update the Final 1,4-DX RE as warranted by the result of that review. In fact, OPPT stated the following, supporting an interpretation that it does not intend to do so:[118]

> EPA views the peer reviewed hazard and exposure assessments and associated risk characterization as robust and upholding the standards of best available science and weight of the scientific evidence per TSCA sections 26(h) and (i).

OPPT's failure to revise its framework analysis of the carcinogenic MOA for 1,4-DX to ensure that it uses the best available science and weight of scientific evidence, as required under TSCA Section 26, has led to erroneous unreasonable risk conclusions in the Final 1,4-DX RE. To illustrate this point, the linear low-dose (non-threshold) point of departure (POD) OPPT used

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115 Lafranconi *et al*. (2023), *supra* note 51, at 13-14.

116 *Id*. at 14.

117 Chappell *et al*. (2021), *supra* note 72, at 39.

118 EPA (2023c) *1,4-Dioxane; Draft Revision to Toxic Substances Control Act (TSCA) Risk Determination; Notice of Availability and Request for Comment*, Agency: Environmental Protection Agency (EPA), Action: Notice, FEDERAL REGISTER, Vol. 88, pp. 48249-48259, at 48254, available at https://www.govinfo.gov/content/pkg/FR-2023-07-26/pdf/2023-15846.pdf.

for quantifying risks to workers must first be placed into context with the non-linear low-dose (threshold) POD used by the ECHA RAC for establishing a protective exposure limit for workers. For example, OPPT calculated a non-threshold inhalation unit risk of 1.0E-06 per $\mu g/m^3$, which it used as the basis for quantifying unreasonable cancer risks and for deriving a lifetime cancer existing chemical exposure limit (EL_{cancer}) (*i.e.*, an occupational exposure limit or OEL) of 0.2 mg/m^3, each with a target risk of 1E-04.[119] In comparison, the ECHA RAC derived a threshold-based POD of 92,000 $\mu g/m^3$ with a benchmark margin of exposure (MOE) of 12.5. The ECHA RAC used these values to derive an OEL that is protective of chronic effects, including cancer, of 7.3 mg/m^3. The effect of these different approaches (*i.e.*, OPPT's use of a linear low-dose approach versus the ECHA RAC's use of a non-linear low-dose approach) are discussed below in the context of risk.

As reported in the Final 1,4-DX RE, OPPT used a linear low-dose extrapolation to evaluate potential cancer risks to workers from 1,4-DX. It concluded that seven of the 10 conditions of use (COU) at the "High-end" exposure estimate present unreasonable risks to workers from inhalation exposures with no respirator and that the unreasonable risks for five of these COUs at the "High-end" exposure estimate would not be mitigated by use of a respirator with an assigned protection factor (APF of 10) (Table 1).[120] OPPT also concluded that the industrial use COU presented unreasonable risk at the "High-end" exposure estimate that would not be mitigated by use of a respirator with an APF of 50.[121] In comparison, we re-evaluated the cancer risks using a threshold approach by applying the ECHA RAC's POD of 92,000 $\mu g/m^3$ and benchmark MOE of 12.5. As shown in Table 2, nine out of 10 COUs at the "High-end" exposure estimate are above the ECHA RAC's benchmark MOE of 12.5 (*i.e.*, no unreasonable risk) with no respirator. The industrial use COU was below the benchmark MOE with no respirator at the "High-end" exposure estimate. These risks were, however, mitigated with a respirator with an APF of 10.[122]

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119 EPA (2023d) *Draft Existing Chemical Exposure Limit (ECEL) for Occupational Use of 1,4-Dioxane*, U.S. Environmental Protection Agency (EPA), 5 pp., at 3, available at https://downloads.regulations.gov/EPA-HQ-OPPT-2022-0905-0039/content.pdf.

120 EPA (2020a), *supra* note 1, at 219.

121 *Id*.

122 *Id*.

Table 1. OPPT's Calculated Cancer Risk Estimates to Workers from Inhalation Exposures Using a Linear Low-Dose (*i.e.*, non-threshold) Extrapolation.[a,b]

	LADC (µg/m^3)		OPPT: Cancer Risk;[c] No respirator; Target Risk = 1E-04		OPPT: Cancer Risk;[d] Respirator with APF 10; Target Risk = 1E-04		OPPT: Cancer Risk;[d] Respirator with APF 50; Target Risk = 1E-04	
Exposure Scenario	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end
Manufacturing	159	3814	**1.6E-04**	**3.8E-03**	1.6E-05	**3.8E-04**	3.2E-06	7.6E-05
Import/Repackaging	1756	1319	**1.8E-03**	**1.3E-03**	**1.8E-04**	**1.3E-04**	3.5E-05	2.6E-05
Industrial Use	1911	9862	**1.9E-03**	**9.9E-03**	**1.9E-04**	**9.9E-04**	3.8E-05	**2.0E-04**
Open System Functional Fluids	0.39	1.5	3.9E-07	1.5E-06	3.9E-08	1.5E-07	7.8E-09	3.0E-08
Spray Foam Application	3.6	5.3	3.6E-06	5.3E-06	3.6E-07	5.3E-07	7.2E-08	1.1E-07
Lab Chemicals	42	2835	4.2E-05	**2.8E-03**	4.2E-06	**2.8E-04**	8.4E-07	5.7E-05
Film Cement	582	1384	**5.8E-04**	**1.4E-03**	5.8E-05	**1.4E-04**	1.2E-05	2.8E-05
Use of Printing Inks (3D)	37	48	3.7E-05	4.8E-05	3.7E-06	4.8E-06	7.4E-07	9.6E-07
Dry Film Lubricant	40	177	4.0E-05	**1.8E-04**	4.0E-06	1.8E-05	8.0E-07	3.5E-06
Disposal	680	2540	**6.8E-04**	**2.5E-03**	6.8E-05	**2.5E-04**	1.4E-05	5.1E-05

[a] As reported by OPPT in Table 4-9 of the Final 1,4-DX RE.[123]
[b] OPPT identified the values in the bolded/shaded cells as having cancer risks that exceed the target risk of 1E-04.
[c] Cancer risk was calculated as follows: "Central Tendency LADC (µg/m^3)" or "High-end LADC (µg/m^3)" × IUR (*i.e.*, 1 × 10-6 per µg/m^3).
[d] Cancer risk with a respirator use was calculated by dividing the cancer risk by the APF.

123 EPA (2020a), *supra* note 1, at 219.

Table 2. Re-calculated Cancer Risk Estimates to Workers from Inhalation Exposures Using a Non-linear (*i.e.*, threshold) Approach with the ECHA RAC's POD of 92,000 µg/m^3 and Benchmark MOE of 12.5.[a,b]

	LADC (µg/m^3)		ECHA RAC: Chronic Risk including cancer; No respirator; Benchmark MOE =12.5		ECHA RAC: Chronic Risk including cancer; Respirator with APF 10; Benchmark MOE =12.5		ECHA RAC: Chronic Risk including cancer Respirator with APF 50; Benchmark MOE =12.5	
Exposure Scenario	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end	Central Tendency	High-end
Manufacturing	159	3814	579	24	5786	241	28931	1206
Import/Repackaging	1756	1319	52	70	524	697	2620	3487
Industrial Use	1911	9862	48	**9**	481	93	2407	466
Open System Functional Fluids	0.39	1.5	235897	61333	2358974	613333	11794872	3066667
Spray Foam Application	3.6	5.3	25556	17358	255556	173585	1277778	867925
Lab Chemicals	42	2835	2190	32	21905	325	109524	1623
Film Cement	582	1384	158	66	1581	665	7904	3324
Use of Printing Inks (3D)	37	48	2486	1917	24865	19167	124324	95833
Dry Film Lubricant	40	177	2300	520	23000	5198	115000	25989
Disposal	680	2540	135	36	1353	362	6765	1811

[a] LADCs as reported by OPPT in Table 4-9 of the Final 1,4-DX RE.[124]
[b] We identified the value in the bolded/yellow highlighted cell as having chronic risks, including cancer, below the benchmark MOE of 12.5.
[c] Chronic risk, including cancer, was calculated as follows: POD (µg/m^3) ÷ "Central Tendency LADC (µg/m^3)" or "High-end LADC (µg/m^3)."
[d] Chronic risk, including cancer, with a respirator use was calculated by multiplying the chronic risk by the APF.

124 *Id.*

The precedential nature of OPPT's linear low-dose conclusions in the Final 1,4-DX RE is also impacting its decision making in more recent actions. For example, OPPT issued the 2023 Draft Supplement, which incorporated the linear low-dose cancer risk estimates from the Final 1,4-DX RE.[125] These cancer risk estimates served as the primary risk drivers in the 2023 Draft Supplement.[126] Below, we discuss a representative example.

OPPT presented its unreasonable risk findings in the 2023 Draft Supplement for cancer only, using exclusively a linear low-dose extrapolation. This was a departure from how OPPT has presented unreasonable risk findings in other final risk evaluations in which EPA included both linear low-dose and threshold cancer calculations. For example, in the Final Risk Evaluation for Carbon Tetrachloride (hereinafter the Final CTC RE), OPPT presented worker cancer risks using a linear low-dose extrapolation and a threshold approach.[127] OPPT also stated in the Final CTC RE that "The unreasonable risk determination is based on the risk estimates derived from both approaches."[128] As shown in Table 3, we estimated risks to workers using both approaches, which changes substantially the risk conclusions for 1,4-DX. For example, OPPT identified unreasonable cancer risks for all COUs when workers are not wearing a respirator, with the exception of the central tendency exposure level for the hydraulic fracturing COU. OPPT also identified unreasonable cancer risks with four of the six COUs at the high-end exposure level when workers are wearing a respirator with an APF of 10. In comparison, when the ECHA RAC values are used, two COUs (*i.e.*, PET byproduct and Hydraulic fracturing) were identified with unreasonable risks when the workers are not wearing respirators. These risks were, however, mitigated when workers used a respirator with an APF of 10.

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125 EPA (2023a), *supra* note 11.

126 *Id*. at 21.

124 *See, e.g.*, EPA (2020b) *Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-) CASRN: 56-23-5*, EPA Document # EPA-740-R1-8014, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency (EPA), 392 pp., at 201-202 and 203-204, available at https://www.epa.gov/sites/default/files/2020-10/documents/1_ccl4_risk_evaluation_for_carbon_tetrachloride.pdf.

128 *Id*. at 250.

Table 3. Estimated Risks to Workers Potentially Exposed to 1,4-DX *via* Inhalation Using OPPT's Linear Low-dose Extrapolation (*i.e.*, 1.0E-03 per mg/m^3; Target Risk = 1E-04) versus the ECHA RAC Non-linear Low-dose Extrapolation (*i.e.*, 92 mg/m^3; Benchmark MOE = 12.5).

COUs	Exposure Level[a]	$LADC_{8\text{-hr-TWA}}$ (mg/m^3)[b]	OPPT: Cancer Risk; No respirator; Target Risk = 1.0E-04[c,d,e]	ECHA RAC: Chronic Risk including cancer; No respirator; Benchmark MOE = 12.5[f,g]	OPPT: Cancer Risk: Respirator with APF = 10; Target Risk = 1.0E-04[c,h]	ECHA RAC: Chronic Risk including cancer; Respirator with APF = 10; Benchmark MOE = 12.5[i]
Manufacture/Domestic Manufacture	CT	0.159	**1.59E-04**	578.6	1.59E-05	5786.2
	HE	3.81	**3.81E-03**	24.1	**3.81E-04**	241.5
Commercial Use/Other Uses (Laundry and Dishwashing Products; Dishwasher Detergent)	CT	0.398	**3.98E-04**	231.2	3.98E-05	2311.6
	HE	1.03	**1.03E-03**	89.3	**1.03E-04**	893.2
Commercial Use/Other Uses (Laudnry and Dishwashing Products; Dish Soap)	CT	0.398	**3.98E-04**	231.2	3.98E-05	2311.6
	HE	1.03	**1.03E-03**	89.3	**1.03E-04**	893.2
Commercial Use/Other Uses (Polyethylene Terephthalate (PET) Byproduct)	CT	1.8	**1.80E-03**	51.1	**1.80E-04**	511.1
	HE	23.18	**2.32E-02**	**4.0**	**2.32E-03**	39.7
Commercial Use/Other Uses (Ethoxylation Process Byproduct)	CT	0.459	**4.59E-04**	200.4	4.59E-05	2004.4
	HE	0.592	**5.92E-04**	155.4	5.92E-05	1554.1
Commercial Use/Other Uses (Hydraulic Fracturing)	CT	0.07	7.00E-05	1314.3	7.00E-06	13142.9
	HE	9.49	**9.49E-03**	**9.7**	**9.49E-04**	96.9
[a] CT = Central Tendency; HE = High-end.						

[b] *See* "Inhalation Exposure" tab at EPA (2023e).[129]
[c] *See* "Bridge Table" tab at EPA (2023e).[130]
[d] OPPT identified the values in the bolded/shaded cells as having cancer risks that exceed the target risk of 1E-04.
[e] Cancer risk was calculated as follows: "$LADC_{8\text{-hr-TWA}}$ (mg/m^3)" CT or HE × IUR (*i.e.*, 1 × 10-3 per mg/m^3).
[f] We identified the values in the bolded/yellow highlighted cells as having chronic risks, including cancer, below the benchmark MOE of 12.5.
[g] Chronic risk, including cancer, was calculated as follows: POD (mg/m^3) ÷ "$LADC_{8\text{-hr-TWA}}$ (mg/m^3)" CT or HE.
[h] Chronic risk, including cancer, with a respirator use was calculated by multiplying the chronic risk by the APF.
[i] Cancer risk with a respirator use was calculated by dividing the cancer risk by the APF.

129 EPA (2023e) *12. 1,4-Dioxane Draft RE - Occupational Exposure and Risk Estimates - public release - July 2023*, , available at https://downloads.regulations.gov/EPA-HQ-OPPT-2022-0905-0008/content.xlsx.

130 *Id*.

We acknowledge that OPPT released the 2023 Draft Supplement for public comment and that submitting comments on that document is the appropriate mechanism. We are, however, mentioning the 2023 Draft Supplement here because OPPT stated in the notice of availability and request for public comment on the 2023 Draft Supplement that it "is not seeking additional review of…[the information in the Final 1,4-DX RE]…as this information has not changed."[131] OPPT is correct that the information in the Final 1,4-DX RE has not changed. However, it should have changed based on the public comments OPPT received on its systematic review used in the draft risk evaluation for 1,4-DX, the feedback OPPT received from NASEM on the 2018 SR Document, additional manuscripts published after the release of the Final 1,4-DX RE, and OPPT's ongoing obligation to comply with the scientific standards under TSCA Section 26.

According to OPPT, it issued the 2023 Draft Supplement according to the requirements of Executive Order 13990, which instructed federal agencies to revisit decisions made between January 21, 2017, and January 21, 2021, to ensure they are "following the science."[132] As we indicated previously, OPPT withdrew the 2018 SR Document; however, it did not suspend, revise, or rescind the risk evaluations, including the Final 1,4-DX RE, that were performed according to the 2018 SR Document. Moreover, OPPT's issuance of its revised risk determination for 1,4-DX indicates the pre-decisional nature of its decision making, given that the public comment period for this document ended on the same day as the public comment period for the 2023 Draft Supplement.[133,134]

OPPT has summarily rejected previous RFCs submitted on its draft and final risk evaluations by providing boilerplate language on the "reiterative public comment opportunities" and statements that OPPT "has concluded that the issues raised in this RFC were appropriately addressed in the TSCA Existing Chemical Evaluation public comment period…".[135,136]

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131 EPA (2023c), *supra* note 118, at 48251.

132 EPA (2023a), *supra* note 11, at 26.

133 EPA (2023c), *supra* note 118, at 48250.

134 EPA (2023a), *supra* note 11, at 43562.

135 *See, e.g.*, EPA (2023f) *Agency Response to Request for Correction 21004*, U.S. Environmental Protection Agency (EPA), 2 pp., at 2, available at https://www.epa.gov/system/files/documents/2023-07/21004_RfC_NMP-RiskEvaluation_EPA-Response_2023-07-27.pdf.

136 *See also* EPA (2023g) *Environmental Protection Agency's Response to RFC 23001*, U.S. Environmental Protection Agency (EPA), 3 pp., at 2, available at

It is well-established that "[a]n agency must consider and respond to significant comments received during the period for public comment."[137] OPPT has failed to do so; therefore, an RFC is the appropriate remaining administrative mechanism.

5. Closing

Based on the above information, we respectfully request that OPPT correct the Final 1,4-DX RE by updating its framework analysis of the carcinogenic MOA for 1,4-DX after it completes a systematic review that complies with the quality standards in EPA's IQA guidelines. We further request that OPPT consider the expert review and conclusions presented in Lafranconi *et al*. (2023) as part of its framework analysis to ensure that OPPT's revisions to its MOA satisfy the scientific standards under TSCA. Finally, we request that EPA share its draft response to this RFC with OMB, prior to releasing its response.[138] EPA's current plan to address RFCs during risk management rulemaking will not address scientific deficiencies in the Final 1,4-DX RE. In fact, EPA's plan contradicts its own IQA guidelines, which state in part "In cases where the Agency disseminates a study, analysis, or other information prior to the final Agency action or information product, it is EPA policy to consider requests for correction prior to the final Agency action…"[139]

https://www.epa.gov/system/files/documents/2023-08/23001_RFC_NMP-Producers-Group_EPA-Response_eSigned_2023-08-15.pdf.

137 *Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 96 (2015).

138 OMB (2019), *Memorandum for the Heads of Executive Departments and Agencies, M-19-15, Subject: Improving Implementation of the Information Quality Act*, Executive Office of the President, Office of Management and Budget (OMB), at 10, available at https://www.whitehouse.gov/wp-content/uploads/2019/04/M-19-15.pdf.

139 EPA (2002b) *supra* note 4, at 32.

We appreciate the opportunity to provide this RFC. We remain committed to working with EPA on the issues outlined in this RFC and look forward to EPA's timely response.

Respectfully submitted,

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Attachment:
Lafranconi *et al*. (2023)