

June 19, 2019

Comments from Academics, Scientists and Clinicians on Initiation of Prioritization Under the Toxic Substances Control Act (TSCA)

Submitted online via *Regulations.gov* to dockets EPA-HQ-OPPT-2019-0131, EPA-HQ-OPPT-2018-0476, and EPA-HQ-OPPT-2018-0462

These comments are submitted on behalf of the undersigned academics, scientists, and clinicians. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support unless indicated otherwise.

We appreciate the opportunity to provide written comments on EPA's initiation of prioritizing existing chemicals pursuant to the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA"). Under amended TSCA, EPA must by December 2019 commence risk evaluations on 20 high priority chemicals that may present an unreasonable risk, and designate 20 low priority chemicals that will not undergo further evaluation at this time.¹ EPA has now put forward 20 high priority and 20 low priority candidate chemicals. At this stage, it is critical for EPA to obtain all reasonably available² information for high priority candidates needed to complete comprehensive, scientifically accurate risk evaluations, including all conditions of use throughout lifecycle. Likewise, EPA needs to obtain reasonably available information on low priority candidates to evaluate whether or not they "may present an unreasonable risk."³

Further, as these are the first priority chemicals EPA is evaluating under amended TSCA, EPA's approach sets a precedent for future evaluations. EPA must proceed with identifying, expeditiously evaluating, and limiting dangerous chemicals from the more than 40,000 existing chemicals on the active TSCA inventory in a manner based on the best available science that will protect our most vulnerable populations.

Our comments address the following main points:

- 1. EPA is mandated to make decisions on high and low priority chemicals based on adequate or sufficient information, respectively. EPA needs to determine the completeness of the database on the 40 candidate priority chemicals and exercise its full authorities to fill data gaps under TSCA sections 4 and 8, and make information public under section 14.**
- 2. The criteria for inclusion on the Safer Chemical Ingredient List (SCIL) do not constitute sufficient data for a low priority designation under TSCA.**
- 3. To establish that a chemical does not have a particular hazard, EPA needs robust empirical data as delineated by established authoritative guidelines.**

¹ 15 USC §2605 (b)(2)(B)

² 15 USC §2625 (k) requires the Administrator to consider all reasonably available information in the prioritization process; EPA's prioritization rule states: "Reasonably available information means information that EPA possesses or can reasonably generate, obtain and synthesize for use, considering the deadlines specified in 15 U.S.C. 2605(b) for prioritization and risk evaluation. Information that meets such terms is reasonably available information whether or not the information is confidential business information that is protected from public disclosure under 15 U.S.C. 2613." The preamble to the rule notes, "EPA agrees that it makes sense to view information that can be obtained through testing as 'reasonably available' ..." 82 FR 33753

³ 15 USC §2605 (b)(1)(B)

4. **EPA should rely on existing Integrated Risk Information System (IRIS) assessments, to be updated by IRIS where needed using its validated systematic review method. EPA should not use “Application of systematic review in TSCA risk evaluations” because it is inconsistent with empirically based methods, and the data quality criteria are arbitrary and not science-based.**
5. **As recommended by the National Academies, EPA should perform cumulative risk evaluations for all chemicals. Additionally, EPA should conduct risk evaluations on groups of chemicals together (such as phthalates or chlorinated solvents) as warranted. EPA should immediately identify and issue orders for data needed to complete such assessments, including data needed to incorporate the effects of other chemicals and non-chemical stressors.**
6. **EPA should proceed immediately with developing the information needed to fill data gaps on the flame retardants TCEP and TBBPA.**

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

Sincerely,

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DETAILED COMMENTS

- 1. EPA is mandated to make decisions on high and low priority chemicals based on adequate or sufficient information, respectively. EPA needs to determine the completeness of the database on the 40 candidate priority chemicals and exercise its full authorities to fill data gaps under TSCA sections 4 and 8, and make information public under section 14.**

TSCA specifies that substances must be designated high priority if the Administrator concludes, without consideration of non-risk factors, that they “may present an unreasonable risk to health or the environment because of potential hazard and a potential route of exposure under the conditions of use.”⁴ Low priority listing is appropriate for substances for which the Administrator concludes there is “sufficient information” to establish that they do “not meet the standard . . . for designating a chemical substance [as] high-priority.”⁵ In other words, to designate a substance low priority, the Agency must find it does not present unreasonable risks to health or the environment, and it must do so based on “sufficient information.”

High priority chemicals, upon designation, will immediately move into the risk evaluation process. For the risk evaluation, both TSCA⁶ and EPA’s regulation⁷ require adequate information to make a determination of whether or not a chemical poses an unreasonable risk. The regulation also requires the evaluation of “relevant” potential human and environmental hazards.⁸

Therefore, “sufficient” information is required for low priority chemicals and “adequate” information is required for high priority chemicals. Further, all relevant health hazards must be evaluated. Certain health hazards are specifically designated in TSCA, indicating that Congress expressly recognized these types of health effects as an unreasonable risk, and envisioned that EPA should assess them: “cancer/ carcinogenesis, mutagenesis/ gene mutation, teratogenesis, behavioral disorders, and birth defects.”⁹ To assess the sufficiency/ adequacy of the data on the 40 candidate chemicals, EPA should compare the completeness of the database on each chemical to existing lists of traits deemed important to assess for chemical safety.

The health hazard dataset needed for EPA’s Design for the Environment (DfE) program to conduct an alternatives assessment is such a data set and is similar to the widely used chemical assessment protocol GreenScreen.^{10,11} The dataset includes the following health endpoints:

1. Acute mammalian toxicity
 - a. Oral
 - b. Dermal
 - c. Inhalation
2. Respiratory sensitization

⁴ 15 USC §2605 (b)(1)(B)

⁵ Id.

⁶ 15 USC §2601 (b)(1)

⁷ 40 CFR § 702.41 (b)

⁸ 40 CFR § 702.41 (d)(3)

⁹ 15 USC §2603 (b)(2)(A); 15 USC §2603 (e); 15 USC §2605 (b)(2)(D)

¹⁰ US EPA (2011) Design for the Environment Alternatives Assessment Criteria for Hazard Evaluation. Available: https://www.epa.gov/sites/production/files/2014-01/documents/aa_criteria_v2.pdf

¹¹ Clean Production Action (2018) GreenScreen for Safer Chemicals. Available: https://www.greenscreenchemicals.org/images/ee_images/uploads/resources/GS_TwoPager_July2018.pdf

3. Skin sensitization
4. Eye irritation/ corrosivity
5. Skin irritation/ corrosivity
6. Carcinogenicity
7. Mutagenicity/ genotoxicity
8. Reproductive and developmental toxicity
9. Developmental neurotoxicity
10. Neurotoxicity
11. Repeated dose toxicity
12. Endocrine activity

Because sufficient or adequate information is critical for decision-making on both low and high priority chemicals, it is imperative that EPA determine the completeness of the database on the 40 candidate chemicals, and quickly move forward with issuing orders to fill identified data gaps.

EPA should describe the key areas where data is lacking for each chemical, and issue orders or rules pursuant to TSCA Section 4 and/ or Section 8 to obtain these data. Section 4 test orders should outline the most relevant test models, exposure pathways, health outcomes, and target populations (including any vulnerable or sensitive populations) anticipated to support the generation of high-quality and relevant evidence to support timely decision-making, as described in point 3 below.

The responses and data received from EPA requests should be made publicly available. TSCA section 14 clearly states that health and safety studies are not considered confidential business information (CBI) and thus are not protected from disclosure. EPA should also provide a public summary characterizing the data and its completeness for each chemical.

2. The criteria for inclusion on the Safer Chemical Ingredient List (SCIL) do not constitute sufficient data for a low priority designation under TSCA.

It is important to note that while all 20 of the low priority chemical candidates are drawn from EPA's SCIL, meeting the criteria for inclusion on the SCIL does not constitute sufficient data for a low priority designation under TSCA because the SCIL does not consider all relevant health hazards and conditions of use throughout the chemical's life cycle as mandated by TSCA. EPA would need to take several additional steps to supplement the SCIL analysis to meet the requirements of TSCA.

First, EPA would need to evaluate additional hazard endpoints for all low priority candidate chemicals, as the Safer Choice Master Criteria include only 8 health and 2 ecological hazard endpoints.¹² Notably missing is endocrine activity, which should be evaluated using a comprehensive protocol such as described in the European Chemicals Agency Guidance (ECHA) for the identification of endocrine disruptors.¹³ High-throughput assays for estrogen receptor (ER) or androgen receptor (AR) bioactivity are inadequate because they have not been sufficiently validated and demonstrated effective in identifying chemicals of concern. The mathematical models used to evaluate data on ER and AR

¹² EPA (2012) EPA's Safer Choice Program Master Criteria for Safer Ingredients. Available: https://www.epa.gov/sites/production/files/2013-12/documents/dfe_master_criteria_safer_ingredients_v2_1.pdf

¹³ ECHA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. Available: <https://www.efsa.europa.eu/en/efsajournal/pub/5311>

bioactivity discounted potential low-dose effects or non-monotonic dose response (NMDR), contrary to recent reports from the National Academies, which specified opportunities to improve data on the evaluation of chemicals for low-dose effects and NMDR.^{14,15} These reports highlight ways that EPA could incorporate more current science and mechanisms for hazard evaluation, particularly for chemicals and classes of chemicals that have the potential to interact with hormonal pathways.

Second, chemicals on the SCIL do not necessarily have data for all the 8 health endpoints included in the Safer Choice Master Criteria. For example, EPA's Safer Choice Criteria for Solvents notes:

“Fully characterized endpoints for all chemicals are optimal. However, insufficient characterization may be acceptable for the endpoints of carcinogenicity and neurotoxicity, because concern is not expected and data are limited, respectively.”¹⁶

This means that a solvent can be included on the SCIL with no available testing data on carcinogenicity. This is clearly inadequate to meet the TSCA mandate of sufficient data to demonstrate no unreasonable risk.

Third, EPA would need to evaluate all conditions of use for each chemical, including reasonably foreseen uses, as only a limited subset of uses related to particular products were evaluated for the SCIL listing.

As detailed above, EPA needs to describe the completeness of the database on all low priority chemical candidates and proceed with orders to fill data gaps, regardless of a chemical's status on the SCIL.

3. To establish that a chemical does not have a particular hazard, EPA needs robust empirical data as delineated by established authoritative guidelines.

In general, absorption, uptake and/ or bioavailability are exposure, not hazard, considerations. Hazard traits are intrinsic properties of chemicals, while bioavailability relates to a chemical's exposure potential. Risk evaluations should assess hazard and exposure separately, and then integrate the information to determine risks, as described in EPA's risk evaluation rule.¹⁷ It is not appropriate for EPA to use expected low absorption, uptake and/ or bioavailability to dismiss potential hazards— lack of hazard can only be demonstrated by robust empirical data, as described below.

Developmental Toxicity

EPA's Guidelines for Developmental Toxicity Risk Assessment note that, in general, short-term developmental toxicity tests (such as OECD 421) are not suitable for use in risk assessment.

“The need for short-term tests for developmental toxicity has arisen from the need to establish

¹⁴ Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals (2017)

¹⁵ Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as they Apply to Endocrine Disruptors (2014)

¹⁶ EPA (year unknown) Safer Choice Criteria for Solvents. Pg. 4. Available: https://www.epa.gov/sites/production/files/2014-02/documents/dfe_screen_for_solvents_in_cleaning_products_february2009.pdf

¹⁷ 40 CFR §702.41

testing priorities for the large number of agents in or entering the environment, the interest in reducing the number of animals used for routine testing, and the expense of testing. These approaches may be useful in making preliminary evaluations of potential developmental toxicity, for evaluating structure activity relationships, and for assigning priorities for further, more extensive testing... However, the Agency currently considers a short-term test as “insufficient” by itself to carry out a risk assessment.”¹⁸ (Emphasis added)

The Guidelines describe the evidence needed to make a determination on developmental toxicity:

“The minimum evidence necessary to judge that a potential hazard exists generally would be data demonstrating an adverse developmental effect in a single, appropriate, well-conducted study in a single experimental animal species. The minimum evidence needed to judge that a potential hazard does not exist would include data from appropriate, well-conducted laboratory animal studies in several species (at least two) which evaluated a variety of the potential manifestations of developmental toxicity and showed no developmental effects at doses that were minimally toxic to the adult.”¹⁹ (Emphasis added)

Accordingly, to determine that a low or high priority candidate chemical is not a developmental toxicant, EPA would need data from well-conducted studies in at least two animal species.

Neurodevelopmental Toxicity

In collaboration with Health Canada, EPA published an updated Developmental Neurotoxicity (DNT) guidance document on “the review and interpretation of submitted DNT data to provide guidance on how to evaluate the quality, the conduct, and resulting data derived from the behavioral methods employed in the OECD and/or EPA DNT Guidelines.”²⁰ The document describes modules including detailed clinical observations, motor activity, acoustic/ auditory startle response, and learning and memory data, which should all be included in a comprehensive evaluation of DNT. The guidance also outlines key principles for the analysis and integration of data, including:

- An agent that produces detectable adverse neurotoxic effects in experimental animal studies is assumed to pose a potential hazard to humans;
- An alteration in behaviors of the offspring, or in the ontogeny of behaviors, is considered to indicate a developmentally neurotoxic change. These may occur with or without neuropathological findings;
- Changes in neuronal organization, structure, or neurochemistry also indicate an effect, with or without accompanying functional effects;
- Data from all potentially relevant studies and effective doses or exposures should be considered in a weight-of-evidence approach to characterizing the potential for developmental neurotoxicity;
- While findings at all dose levels are important, those occurring at doses below levels associated with maternal or general toxicity are generally considered of increased concern;

¹⁸ US EPA (Dec 1991) Guidelines for Developmental Toxicity Risk Assessment. Pp. 19. Available: https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf

¹⁹ US EPA (Dec 1991) Guidelines for Developmental Toxicity Risk Assessment. Pp. 40.

²⁰ NAFTA Technical Working Group on Pesticides. (2016) Developmental Neurotoxicity Study Guidance Document. Pg. 3. Available: https://www.epa.gov/sites/production/files/2017-02/documents/developmental_neurotoxicity_study_internal_guidance_document_final_0.pdf

- While an understanding of toxic mechanisms or pathways can inform an overall evaluation, the lack of such information does not preclude a determination of risk.²¹
- Dose-response is a key indicator of a treatment-related effect; however, there is currently discussion on the relevance of non-monotonic dose-response curves...In the face of a weak or absent dose-response (i.e., no gradation of effect), the pattern of individual animal data should be examined to identify changes in incidence or severity of an effect that may have been present but not reflected in the group data.²²
- Biologically significant, treatment-related findings may occur in the absence of statistical significance.²³

In addition to using the Guidelines for Developmental Toxicity Risk Assessment referenced above, EPA should apply these established principles in making its determination on neurodevelopmental toxicity.

Reproductive Toxicity

EPA's Guidelines for Reproductive Toxicity Risk Assessment note that a prolonged treatment period is required to assess reproductive effects:

"To evaluate adequately the potential effects of an agent on the reproductive systems, a prolonged treatment period is needed. For example, damage to spermatogonial stem cells will not appear in samples from the cauda epididymis or in ejaculates for 8 to 14 weeks, depending on the test species. With some chemical agents that bioaccumulate, the full impact on a given cell type could be further delayed, as could the impact on functional endpoints such as fertility. In such situations, adequacy of the dosing duration is a critical factor in the risk assessment."²⁴

The Guidelines additionally note that screening tests (including OECD 421) limited to one generation are not suitable for risk assessment:

"Several shorter-term reproductive toxicity screening tests have been developed. Among those are the Reproductive/Developmental Toxicity Screening Test, which is part of the OECD's Screening Information Data Set protocol (Scala et al., 1992; Tanaka et al., 1992; OECD, 1993a), a tripartite protocol developed by the International Conference on Harmonization (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use, 1994; Manson, 1994), and the NTP's Short-Term Reproductive and Developmental Toxicity Screen (Harris, M.W. et al., 1992). These protocols have been developed for setting priorities for further testing and should not be considered sufficient by themselves to establish regulatory exposure levels. Their limited exposure periods do not allow assessment of certain aspects of the reproductive process, such as developmentally induced effects on the reproductive systems of offspring, that are covered by the multigeneration reproduction protocols."²⁵ (Emphasis added)

The Guidelines describe the evidence needed to make a determination on reproductive toxicity:

²¹ Id. pg. E-3

²² Id. pg. E-5

²³ Id. pg. E-8

²⁴ US EPA (Oct 1996) Guidelines for Reproductive Toxicity Risk Assessment. Pp. 7 Available: https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf

²⁵ US EPA (Oct 1996) Guidelines for Reproductive Toxicity Risk Assessment. Pg. 12

“The minimum evidence necessary to determine if a potential hazard exists would be data demonstrating an adverse reproductive effect in a single appropriate, well-executed study in a single test species. The minimum evidence needed to determine that a potential hazard does not exist would include data on an adequate array of endpoints from more than one study with two species that showed no adverse reproductive effects at doses that were minimally toxic in terms of inducing an adverse effect. Information on pharmacokinetics, mechanisms, or known properties of the chemical class may also strengthen the evidence.”²⁶ (Emphasis added)

Accordingly, to determine that a low or high priority candidate chemical is not a reproductive toxicant, EPA would need data from well-conducted studies in at least two animal species.

Carcinogenicity

According to the EPA Cancer Guidelines, a determination of “Not Likely to Be Carcinogenic to Humans” requires robust evidence as follows:

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

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

A descriptor of “not likely” applies only to the circumstances supported by the data. For example, an agent may be “Not Likely to Be Carcinogenic” by one route but not necessarily by another. In those cases that have positive animal experiment(s) but the results are judged to be not relevant to humans, the narrative discusses why the results are not relevant.”²⁷

Therefore, to determine that a low or high priority candidate chemical is not likely to be a carcinogen, supporting data from male and female animals of at least two species in well-designed and conducted studies would be required.

Endocrine Activity

²⁶ Id. pp. 72

²⁷ US EPA (2005) Guidelines for Carcinogen Risk Assessment. Pp. 84-85. Available from: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

ECHA's guidance for the identification of endocrine disruptors describes what is needed for a sufficient data set to support the absence of adverse effects on estrogenic, androgenic, thyroidal and steroidogenic modalities (EATS).²⁸ The dataset includes:

- For estrogenic, androgenic and steroidogenic modalities: Extended one-generation reproductive toxicity study (OECD TG 443; with cohort 1a/1b including the mating of cohort 1b to produce the F2 generation)²⁹ or a two-generation reproductive toxicity study (OECD TG 416; test protocol according to latest version of January 2001)³⁰
- For thyroidal modalities: OECD test guidelines 407, 408, 409 (and/or the one-year dog study, if available), 416 (or 443 if available) and 451-3 with thyroid parameters included.

To determine that a low or high priority candidate chemical does not have endocrine activity, EPA needs data as described by ECHA to demonstrate a lack of adverse endocrine effects.

4. EPA should rely on existing Integrated Risk Information System (IRIS) assessments, to be updated by IRIS where needed using its validated systematic review method. EPA should not use "Application of systematic review in TSCA risk evaluations" because it is inconsistent with empirically based methods, and the data quality criteria are arbitrary and not science-based.

The National Academies of Sciences (NAS) 2017 report on implementation of systematic review³¹ recommends that EPA should build on existing high-quality reviews to incorporate new studies, and then use this updated systematic review as a basis for its assessment. There are existing IRIS assessments for 14 of the 20 high priority candidate chemicals (see Table 1); though these are not systematic reviews, they are authoritative assessments that have gone through the Agency's peer-review process, public comment, and in some cases NAS review.

Table 1. Existing IRIS assessments for high priority candidate chemicals.

Chemical (CAS RN)	Date of last IRIS update (Link to IRIS assessment)
p-Dichlorobenzene (106-46-7)	Jan 1994 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=552)
1,2-Dichloroethane (107-06-2)	Mar 1987 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=149)
trans-1,2-Dichloroethylene (156-60-5)	Sept 2010 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=314)
o-Dichlorobenzene (95-50-1)	Nov 1990 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=408)

²⁸ ECHA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. Pg. 31-32. Available: <https://www.efsa.europa.eu/en/efsajournal/pub/5311>

²⁹ OECD (2012) Test No. 443: Extended One-Generation Reproductive Toxicity Study. In: OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. 25 pp. <https://doi.org/10.1787/9789264185371-en>

³⁰ OECD (2001) Test No. 416: Two-Generation Reproduction Toxicity. In: OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. 13 pp. <https://doi.org/10.1787/9789264070868-en>

³¹ The National Academies of Sciences. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*. Washington, D.C.: National Academies Press; 2017.

1,1,2-Trichloroethane (79-00-5)	Sept 1988 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=198)
1,2-Dichloropropane (78-87-5)	Dec 1991 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=601)
1,1-Dichloroethane (75-34-3)	Oct 1990 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=409)
Dibutyl phthalate (DBP) (84-74-2)	Oct 1990 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=38)
Butyl benzyl phthalate (BBP) (85-68-7)	Sept 1989 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=293)
Di-ethylhexyl phthalate (DEHP) (117-81-7)	Sept 1988 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=14)
Ethylene dibromide (106-93-4)	Jul 2004 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=361)
1,3-Butadiene (106-99-0)	Nov 2002 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=139)
Formaldehyde (50-00-0)	Sept 1990 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=419)
Phthalic anhydride (85-44-9)	Sept 1988 (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=308)

EPA should use these IRIS assessments as the foundation for its evaluation and ask IRIS to update and incorporate new evidence where needed. For the phthalates, multiple systematic reviews have recently been published which need to be incorporated.^{32,33,34}

In general, EPA should use one of the three existing empirically-based systematic review methodologies below for its TSCA risk evaluations. Having been peer-reviewed, validated, demonstrated in case studies and recommended for chemical evaluations by the NAS,³⁵ these are the best available science for systematic review:

³² Yost, E. E., Euling, S. Y., Weaver, J. A., Beverly, B. E. J., Keshava, N., Mudipalli, A., ... Makris, S. L. (2018). Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies. *Environment International*. <https://doi.org/10.1016/J.ENVINT.2018.09.038>

³³ Radke, E. G., Braun, J. M., Meeker, J. D., & Cooper, G. S. (2018). Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. *Environment International*, 121(Pt 1), 764–793. <https://doi.org/10.1016/j.envint.2018.07.029>

³⁴ Radke, E. G., Galizia, A., Thayer, K. A., & Cooper, G. S. (2019). Phthalate exposure and metabolic effects: a systematic review of the human epidemiological evidence. *Environment International*, 104768. <https://doi.org/10.1016/J.ENVINT.2019.04.040>

³⁵ The National Academies of Sciences. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*. Washington, D.C.: National Academies Press; 2017.

- Navigation Guide: Woodruff TJ, Sutton P. *The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes*. Environ Health Perspect. 2014;122(10):1007-1014. doi:10.1289/ehp.1307175.
- OHAT: National Toxicology Program Office of Health Assessment and Translation. *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration*. National Institute of Environmental Health Sciences; 2015
- Integrated Risk Information System (IRIS): National Academies of Sciences, Engineering, and Medicine. 2018. *Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25086>.

Our previous comments provide detailed evidence on the scientific shortcomings of the TSCA method, “Application of systematic review in TSCA risk evaluations” (Appendix A) and why it should not be used. Additionally, we have published a peer-reviewed commentary³⁶ in the *American Journal of Public Health* highlighting the scientific and technical flaws in the TSCA method (Appendix B).

Finally, for formaldehyde, EPA needs to immediately release the recently updated IRIS assessment for public comment and NAS review. A 2019 report from the Government Accountability Office raised concerns about EPA leadership’s unexplained directive to stop the release of the formaldehyde assessment.³⁷ EPA must release the assessment so that the TSCA office can directly utilize the extensive work already done by NAS and IRIS scientists. The NAS’ most recent review of the IRIS program’s implementation of systematic review found it to be robust.³⁸

5. As recommended by the National Academies, EPA should perform cumulative risk evaluations for all chemicals. Additionally, EPA should conduct risk evaluations on groups of chemicals together (such as phthalates or chlorinated solvents) as warranted. EPA should immediately identify and issue orders for data needed to complete such assessments, including data needed to incorporate the effects of other chemicals and non-chemical stressors.

The NAS defines cumulative risk broadly to mean the risk posed by multiple chemicals and other stressors that cause varied health effects and to which people are exposed by multiple pathways and exposure routes and for varied durations.³⁹ Cumulative risk is especially critical for susceptible and more highly exposed sub-populations, who generally face greater chemical exposures (more chemicals, higher levels, and higher frequency) as well as non-chemical stressors.⁴⁰ The NAS found that “Where single-

³⁶ Singla, V. I., Sutton, P. M., & Woodruff, T. J. (2019). The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health. *American Journal of Public Health*, 109(7), 982–984. <https://doi.org/10.2105/AJPH.2019.305068>

³⁷ US GAO (2019) Chemical Assessments: Status of EPA’s Efforts to Produce Assessments and Implement the Toxic Substances Control Act. Available: <https://www.gao.gov/assets/700/697212.pdf>

³⁸ National Academies of Sciences, Engineering, and Medicine. 2018. *Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25086>.

³⁹ National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Pg. 4 Retrieved from <http://site.ebrary.com/id/10274055>

⁴⁰ Solomon, G. M., Morello-Frosch, R., Zeise, L., & Faust, J. B. (2016). Cumulative Environmental Impacts: Science and Policy to Protect Communities. *Annual Review of Public Health*, 37(1), 83–96. <https://doi.org/10.1146/annurev-publhealth-032315-021807>

chemical risk assessments might yield the verdict ‘absence of risk,’ dose addition might yield the opposite conclusion.”⁴¹ Additionally, effects of toxic chemicals can be compounded by non-chemical stressors such as socio-economic status.

The NAS specifically recommended “that a cumulative risk assessment be conducted for phthalates and that the assessment include other antiandrogens.”⁴² This is because the NAS found that “The current practice of restricting cumulative risk assessment to structurally or mechanistically related chemicals ignores the important fact that different chemical exposures may result in the same common adverse outcomes.”⁴³

Therefore, EPA should conduct a cumulative risk assessment for phthalates, chlorinated solvents, and any other chemicals that may contribute to common adverse health outcomes. For all chemicals, it is critical that EPA incorporate information on non-chemical stressors in this cumulative assessment to ensure that the most vulnerable populations, including those living in poverty, are accounted for in the evaluation of risk.

For its evaluations, EPA should draw on relevant reviews and publications, such as the Consumer Product Safety Commission’s Chronic Hazard Advisory Panel on phthalates.⁴⁴

6. EPA should proceed immediately with developing the information needed to fill data gaps on the flame retardants TCEP and TBBPA.

In March 2017⁴⁵ and April 2017⁴⁶, EPA responded to TSCA section 21 petitions that requested testing on the flame retardants TBBPA and TCEP (included in the chlorinated phosphate esters cluster, CPEs). In its response, EPA identified data, model development and other critical types of information needed to characterize hazard and exposure for these chemicals (see Appendix C). EPA should proceed immediately with the scientific work, section 4 test orders, section 8 rules, and/ or other activities needed to fill data gaps and generate adequate information for risk evaluation of TCEP and TBBPA.

These include:

- Assessing whether available toxicity, toxicokinetic, absorption, distribution, metabolism, and excretion (ADME) data are appropriate for conducting route-to-route extrapolation for exposure pathways that do not have adequate empirical data. If not, EPA should use its authorities to generate the needed data as described in point 1 above. Inhalation, dermal and oral exposure pathways are all significant sources of exposure for both TCEP and TBBPA and all three pathways must be included in the risk evaluations.

⁴¹ National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Pg. 8 Retrieved from <http://site.ebrary.com/id/10274055>

⁴² Id. pg 7

⁴³ Id. pg. 10

⁴⁴ Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: <http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf>

⁴⁵ 82 FR 14171

⁴⁶ 82 FR 17601

- Requesting data and consultation from other Agencies that have conducted key relevant exposure and toxicity studies, and assessing whether these data are adequate for EPA's risk evaluation purposes, especially as related to occupational exposures. If not, EPA should use its authorities to generate the needed data as described in point 1 above. Sources include those identified in EPA's petition responses as well as new studies conducted since 2017 including, but not limited to: National Institute of Occupational Safety and Health (NIOSH);⁴⁷ Centers for Disease Control and Prevention (CDC);⁴⁸ National Toxicology Program;⁴⁹ and US Geological Survey (USGS).⁵⁰
- Assessing whether available water monitoring data are adequate to quantify environmental releases from non-industrial and consumer uses of TCEP. EPA identifies data on flame retardant water concentrations from USGS, peer-reviewed studies and other countries as potentially sufficient to assess risk related to water contamination from these sources. If not, EPA should use its authorities to generate the needed data as described in point 1 above.
- Collecting data on recycling and disposal facilities (including incineration) necessary to quantify risk associated with related worker and community exposures, such as: number and location of facilities, types and volumes of products processed, and recycling and/or disposal methods employed at each; and assessment of whether data collected at recycling and disposal facilities in other countries are comparable to data collected in the U.S. EPA also needs to assess the sufficiency of available data on incineration byproducts, including brominated/ chlorinated dioxins, furans and polycyclic aromatic hydrocarbons. If any of these data are not adequate, EPA should use its authorities to generate the needed data as described in point 1 above.

⁴⁷ NIOSH (2014) Assessment of Occupational Exposure to Flame Retardants.

⁴⁸ CDC (2019) Evaluation of Exposure to Metals and Flame Retardants at an Electronics Recycling Company. HHE Report No. 2016-0257-3333. Available: <https://www.cdc.gov/niosh/hhe/reports/pdfs/2016-0257-3333.pdf>

⁴⁹ NTP (1991) Reproductive Toxicity of Tris(2-chloroethyl)phosphate in CD-1 Swiss Mice. Available: <https://ntp.niehs.nih.gov/testing/types/repro/abstracts/rac92040/index-94.html>

⁵⁰ United States Geological Survey (USGS). National Water Information System. <https://waterdata.usgs.gov/nwis>

Appendices:

Appendix A: Comments from Academics, Scientists, and Clinicians on: The Application of Systematic Review in TSCA Risk Evaluations

Appendix B: Commentary in *American Journal of Public Health*

Appendix C: Federal register responses to petitions

Appendix A: Comments from Academics, Scientists, and Clinicians on: The Application of Systematic Review in TSCA Risk Evaluations

August 16, 2018

Comments from Academics, Scientists and Clinicians on: The Application of Systematic Review in TSCA Risk Evaluations.

Submitted online via *Regulations.gov* to docket EPA-HQ-OPPT-2018-0210

These comments are submitted on behalf of the undersigned academic, scientists, and clinicians. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical under consideration in these risk evaluations. The co-signers' institutional affiliations are included for identification purposes only and do not necessarily imply any institutional endorsement or support, unless indicated otherwise.

We appreciate the opportunity to provide written comments on the Application of Systematic Review in TSCA Risk Evaluations,^a pursuant to the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety of the 21st Century Act (Lautenberg TSCA). TSCA requires that EPA make decisions about chemical risks based on the "best available science" and the "weight of the scientific evidence"^b which EPA defined in regulation as "...a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance."^c

Systematic review methods originated more than 40 years ago in psychology. The methodology was soon adapted to evaluating the effectiveness of clinical interventions in medicine and related disciplines in response to empirical evidence demonstrating the need to apply scientific principles not only to primary research, but also to research synthesis methods that inform decision-making in healthcare (1-3). Almost a decade ago, these empirically-proven methods for research synthesis were adapted to environmental health (4, 5). To date, science-based methods for systematic review in environmental health have been demonstrated in case studies in the peer-reviewed literature (6-13), and adopted by the National Toxicology Program (14) and the U.S. EPA's Integrated Risk Information System (IRIS) program (15).

EPA's systematic review framework under TSCA establishes EPA's "rules" for assembling and interpreting the scientific evidence on chemicals in commerce. These "rules" will determine, whether explicitly, implicitly, and/or by default, *what* evidence EPA will consider, and *how* it will evaluate that evidence when it is making decisions about potentially hazardous chemicals in commerce. Exposure to industrial, commercial, and consumer product chemicals is ubiquitous from the time of conception until death. As such, EPA's rules for gathering and interpreting the science that evaluates the relationship between these exposures and adverse health effects are of profound importance to the general public, and will have even greater impact on the potentially exposed or susceptible sub-populations Congress explicitly mandated EPA to protect: pregnant women, children, individuals with underlying health conditions, workers, and those with greater exposure and/or greater vulnerability to chemical toxicity and exposure.

^a 83 FR 26998, June 11, 2018

^b 15 USC §2625 (h)-(i)

^c 40 CFR 704.33

With so much at stake, we are deeply concerned by EPA's ad hoc and incomplete TSCA systematic review framework, which is inconsistent with current, established, best available empirical methods for systematic review. Moreover, as we detail below, the application of EPA's TSCA framework would likely result in the exclusion of quality research from EPA's decision-making. Accordingly, the TSCA systematic review method does not meet the mandate of the law to use the "best available science."^d

Based on the most current empirically demonstrated principles of systematic review methods, we provide EPA with concrete recommendations and approaches to correct its methodology and inform timely science-based decision-making to achieve the Agency's mission of protecting the public from harmful chemicals.

Our comments address the following six main points:

- 1. EPA's TSCA systematic review framework is ad hoc, incomplete, and does not follow established methods for systematic review that are based on the best available science.**

We recommend: EPA should implement a systematic review method that is compatible with empirically based existing methods and aligns with the Institute of Medicine's^e definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods for every step of the review. EPA should consider methods demonstrated for use in environmental health, and which have been endorsed and utilized by the National Academy of Sciences, i.e., the National Toxicology's Office of Health Assessment and Translation systematic review method, and the Navigation Guide Systematic Review Method. EPA's TSCA systematic review framework should be peer-reviewed by qualified external experts in the field.

- 2. EPA's TSCA systematic review framework utilizes a quantitative scoring method that is incompatible with the best available science in fundamental ways:**
 - a. Quantitative scores for assessing the quality of an individual study are arbitrary and not science-based; the Cochrane Collaboration and National Academy of Sciences recommend against such scoring methods.**
 - b. EPA's scoring method wrongly conflates how well a study is reported with how well the underlying research was conducted; and**
 - c. EPA's scoring method excludes research based on one single reporting or methodological limitation.**

We recommend: EPA should not use a quantitative scoring method to assess quality in individual studies; it should not conflate study reporting with study quality; and it should not exclude otherwise quality research based on a single reporting or methodological limitation. Rather EPA should employ a scientifically valid method to assess risk of bias of individual studies.

- 3. EPA's TSCA systematic review framework does not consider financial conflicts of interest as a potential source of bias in research.**

^d 15 USC §2625 (h)

^e The Institute of Medicine is now the National Academy of Medicine.

We recommend: EPA should assess study and author funding source as a risk of bias domain for individual studies.

4. **The literature review step of EPA's TSCA systematic review framework incorporates select best practices, but also falls short of, or is unclear about, many other best practices for conducting a systematic and transparent literature review.**

We recommend: EPA should make its framework for conducting a literature review congruent with all of the Institute of Medicine's best practices and explicitly include rules for when the list of relevant studies will be considered final.

5. **EPA's TSCA systematic review framework correctly recognizes that mechanistic data are not required for a hazard assessment, but EPA is not clear that these data, if available, can only be used to increase, and not to decrease, confidence in a body of evidence.**

We recommend: EPA should be explicit that mechanistic data can only be used to upgrade a hazard classification, or increase the confidence of a finding made based on evaluation of animal and human data, and that these data will not be used to decrease confidence in a body of evidence.

6. **EPA's TSCA systematic review framework is not independent of the regulatory end user of the review.**

We recommend: EPA's TSCA systematic reviews should be produced independently of the regulatory end user of the review.

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

Sincerely,

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DETAILED COMMENTS

1. EPA's TSCA systematic review framework is ad hoc, incomplete, and does not follow established methods for systematic review that are based on the best available science.

The best available scientific method for a systematic review (SR) specifies that all components of a review be established in a publically available protocol written *prior* to conducting the review to minimize bias and to ensure transparency in decision-making. For example, the Institute of Medicine defines a systematic review as a “scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies” (emphasis added) (16)(p.1). A fatal flaw in EPA's SR framework is that it lacks essential SR elements, including but not limited to: (1) a protocol for executing a SR developed *prior* to conducting the SR; (2) an explicit method for evaluating the overall body of each evidence stream, i.e., animal, human, etc.; and (3) an explicit method for integrating two or more streams of evidence, including defined criteria for the type and level of evidence needed for a decision by EPA.

Notably, EPA's TSCA SR Framework presents a diagram of a complete SR framework in Figure 3-1 (page 15) and states in footnote 4 on that page that the:

Diagram depicts systematic review process to guide the first ten TSCA risk evaluations. It is anticipated that the same basic process will be used to guide future risk evaluations with some potential refinements reflecting efficiencies and other adjustments adopted as EPA/OPPT gains experience in implementing systematic review methods and/or approaches to support risk evaluations within statutory deadlines (e.g., aspects of protocol development would be better defined prior to starting scoping/problem formulation).

However, EPA's TSCA SR Framework then proceeds to describe an ad hoc and highly flawed method limited to only the data collection and, to a limited extent, the data evaluation components of a SR. Specifically, Figure S-1 below, excerpted from the National Academy of Sciences 2014 review of the EPA IRIS program's systematic review method (17), presents all of the components of a science-based SR. The red box indicates the parts of a SR method that EPA has included in its proposed framework.

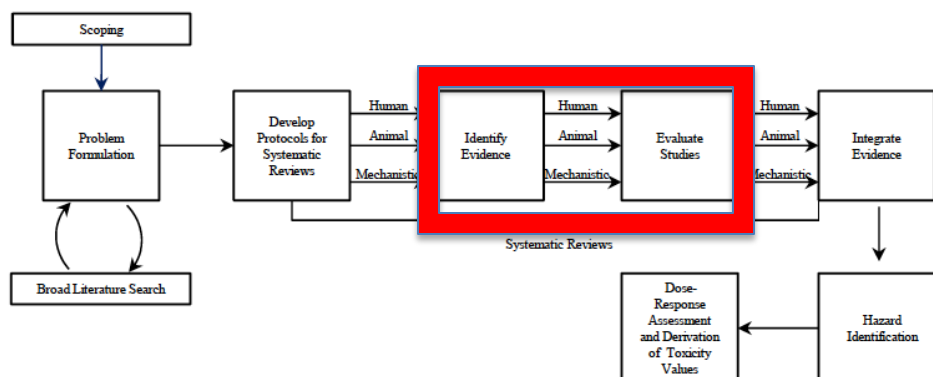


FIGURE S-1 Systematic review in the context of the IRIS process. The committee views public input and peer review as integral parts of the IRIS process, although they are not specifically noted in the figure.

EPA’s piecemeal approach is not only in direct contradiction with the best available scientific methods for SR, but also incompatible with the regulatory definition of “weight of evidence” in the risk evaluation rule, which specifies a complete method spelled out in a protocol developed *before* conducting the review. Therefore, the TSCA systematic review method violates both TSCA statute and regulation.^g

EPA explicitly states that it is proceeding with its first ten risk assessments in the absence of a pre-defined protocol and a complete method for systematic review. Specifically, EPA’s SR Framework states:

(p. 9) ... the purpose of the document is internal guidance that ... sets out general principles to guide EPA’s application of systematic review in the risk evaluation process for the first ten chemicals ... **EPA had limited ability to develop a protocol document detailing the systematic review approaches and/or methods prior to the initiation of the risk evaluation process for the first ten chemical substances. For these reasons, the protocol development is staged in phases while conducting the assessment work” (emphasis added).** Additional details on the approach for the evidence synthesis and integration will be included with the publication of the draft TSCA risk evaluations.

In effect, EPA is saying it does not have time to comply with its regulatory requirement to conduct a science-based systematic review, and will not actually develop its protocol until it completes the first ten systematic reviews.

First, this approach is in clear violation with scientifically-validated approaches to conducting systematic reviews. In its review of the EPA’s Integrated Risk Information System (IRIS) program’s proposed SR methods, the National Academy of Sciences specified that, “Completing the literature search as part of

^f EPA’s risk evaluation rule (40 CFR 704.33) states: “Weight of the 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.”

^g 15 USC §2625 (h)-(i) and 40 CFR 704.33

protocol development is inconsistent with current best practices for systematic review, and the IRIS program is encouraged to complete the public-comment process and finalize the protocol before initiating the systematic review” (15)(Pg. 8). In the case of TSCA risk assessments, EPA is not only completing the literature search as part of protocol development, it is completing the entire systematic review in the absence of a protocol and complete method. It is blatantly biased to write the rules of evidence assembly and interpretation at the same time one is applying the rules, and as such, this method cannot be validly referred to as a science-based systematic review.

Second, a lack of time is not a credible rationale for EPA’s failure to conduct a science-based systematic review for the first ten TSCA chemicals. There are multiple well-developed, science-based, peer-reviewed and validated methods for conducting systematic reviews in environmental health that EPA could readily apply, including the SR method and handbook developed by the Office of Health Assessment and Translation at the National Toxicology Program (14), and the Navigation Guide Systematic Review Method, which has been demonstrated in six case studies (6-13). The National Academy of Sciences cited both of these SR methods as exemplary of the type of methods EPA should use in hazard and risk assessment (17, 18). Further, the National Academy of Sciences utilized both methods in its 2017 assessment of the potential health impacts of endocrine active environmental chemicals (19). Specifically, in its 2017 review the National Academy of Sciences found:

The two approaches [OHAT and Navigation Guide] are very similar ... and they are based on the same established methodology for the conduct of systematic review and evidence assessment (e.g., Cochrane Collaboration, AHRQ Evidence-based Practice Center Program, and GRADE). Both the OHAT and Navigation Guide methods include the key steps recommended by a previous National Academies committee (NRC 2014) for problem formulation, protocol development, specifying a study question, developing PECO statement, identifying and selecting the evidence, evaluating the evidence, and integrating the evidence” (19)(page 119).

Protocols developed for applying the Navigation Guide and the OHAT method have been published and can serve as a template to further expedite EPA’s TSCA reviews.^h

Furthermore, the language of EPA’s systematic review framework is confusing, contradictory, and poorly and incorrectly referenced with little science or policy foundation. This suggests the authors of EPA’s TSCA Systematic Review Framework lack sufficient understanding of the scientific process integral to this work. A particularly egregious example is EPA’s stated understanding of EPA’s TSCA statutory science standards:

(Pg. 26) EPA/OPPT is required by TSCA to use the weight of the scientific evidence in TSCA risk evaluations. Application of weight of evidence analysis is an integrative and interpretive process that considers both data/information in favor (e.g., positive study) or against (e.g., negative study) a given hypothesis within the context of the assessment question(s) being evaluated in the risk evaluation.

This directly contradicts EPA’s own published rule which defines what a systematic review is (see

^h All Navigation Guide systematic review protocols can be found at: <https://prhe.ucsf.edu/navigation-guide> The National Toxicology Program’s protocol for its systematic review to evaluate the evidence for an association between exposure to PFOA or PFOS and immunotoxicity or immune-related health effects is at: https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/protocol_201506_508.pdf

footnote “e”, above) and such an understanding completely subverts the purpose of a systematic review which is to explicitly avoid a simplistic analysis that would lead to erroneous conclusions along the lines of stating that, for instance, “five studies are in favor (positive) and ten are against (negative) and therefore the weight is ...”

Another bewildering statement by EPA concerns its highly quantitative scoring method, which is the main topic of its systematic review framework (see comment #2, below). EPA adds a caveat to the scoring method that says quantitative scoring is actually a qualitative method, and further: “The [scoring] system is not intended to imply precision and/or accuracy of the scoring results” (Pg. 35).

The ad hoc and incomplete nature of EPA’s systematic review framework is incompatible in many additional fundamental ways, described further in detail below, with science based methods of systematic review developed, endorsed, and/or advanced by the: National Academy of Sciences (17-19); the Institute of Medicine (16); the National Toxicology Program (14); the Cochrane Collaboration (20); the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method (21, 22); the international scientific collaboration that developed a framework for the “systematic review and integrated assessment” (SYRINA) of endocrine disrupting chemicals (23); the SYRCLE systematic review method for animal studies (24); the Campbell Collaboration’s methods (25); and the Navigation Guide systematic review method developed by a collaboration of scientists led by the University of California San Francisco (4). Most of these organizations also pre-publish their protocols either online (i.e., the National Toxicology Program) or in PROSPEROⁱ (i.e., UCSF).

We recommend: EPA should implement a systematic review method that is compatible with empirically based existing methods and aligns with the Institute of Medicine’s definition of a systematic review, including, but not limited to, using explicit and pre-specified scientific methods for every step of the review. EPA should consider methods demonstrated for use in environmental health, and which have been endorsed and utilized by the National Academy of Sciences, i.e., the National Toxicology’s Office of Health Assessment and Translation systematic review method, and the Navigation Guide Systematic Review Method. EPA’s TSCA systematic review framework should be peer-reviewed by qualified external experts in the field.

ⁱ PROSPERO International prospective register of systematic reviews <https://www.crd.york.ac.uk/prospero/>

2. EPA's TSCA systematic review framework utilizes a quantitative scoring method that is incompatible with the best available science in fundamental ways:

- a. Quantitative scores for assessing the quality of an individual study are arbitrary and not science-based; the Cochrane Collaboration and National Academy of Sciences recommend against such scoring methods.
- b. EPA's scoring method wrongly conflates how well a study is reported with how well the underlying research was conducted; and
- c. EPA's scoring method excludes research based on one single reporting or methodological limitation.

A detailed explanation of each of these scientific shortcomings is provided below.

(a) Quantitative scores for assessing the quality of an individual study are arbitrary and not science-based.

EPA's SR framework employs a quantitative scoring method to assess the quality of individual studies, assigning, based on its "professional judgment", various weights for quality domains and then summing up the quantitative scores to decide whether a study is of "high", "medium", or "low" quality as follows:^j

(Pg. 33) A numerical scoring method is used to convert the confidence level for each metric into the overall quality level for the data/information source. The overall study score is equated to an overall quality level (*High*, *Medium*, or *Low*) using the level definitions and scoring scale shown in Table A-1. The scoring scale was obtained by calculating the difference between the highest possible score of 3 and the lowest possible score of 1 (i.e., $3-1=2$) and dividing into three equal parts ($2 \div 3 = 0.67$). This results in a range of approximately 0.7 for each overall data quality level, which was used to estimate the transition points (cut-off values) in the scale between *High* and *Medium* scores, and *Medium* and *Low* scores. These transition points between the ranges of 1 and 3 were calculated as follows: Cut-off values between *High* and *Medium*: $1 + 0.67 = 1.67$, rounded up to 1.7 (scores lower than 1.7 will be assigned an overall quality level of *High*) Cut-off values between *Medium* and *Low*: $1.67 + 0.67 = 2.34$, rounded up to 2.3 (scores between 1.7 and lower than 2.3 will be assigned an overall quality level of *Medium*)

This overall scoring method is applied to all streams of evidence, and our comments reflect our objection to EPA's applying scoring to any and all streams of evidence.^k

Illustrative of the scoring method, in Appendix H "Data Quality Criteria for Epidemiologic Studies," (page

^j See Appendix A for a more detailed description of the scoring method; how the method will be applied specifically to various streams of evidence, i.e., occupational exposure and release data; animal and in vitro data; epidemiologic studies; etc., is described in subsequent Appendices B-H.

^k EPA's framework applies quantitative scoring to all types of data; EPA/OPPT "is not applying weighting factors to the general population, consumer, and environmental exposure data types. In practice, it is equivalent to assigning a weighting factor of 1, which statistically assumes that each metric carries an equal amount of weight." (Pg. 96).

225) EPA presents how scoring is further applied to human studies, explaining:

The critical metrics within each domain are those that cover the most important aspects of the domain and are those that more directly evaluate the role of confounding and bias. After pilot testing the evaluation tool, EPA recognized that more attention (or weight) should be given to studies that measure exposure and disease accurately and allow for the consideration of potential confounding factors. Therefore, metrics deemed as critical metrics are those that identify the major biases associated with the domain, evaluate the measurement of exposure and disease, and/or address any potential confounding. ... EPA/OPPT assigned a weighting factor that is twice the value of the other metrics within the same domain to each critical metric. Remaining metrics are assigned a weighting factor of 0.5 times the weighting factor assigned to the critical metric(s) in the domain. The sum of the weighting factors for each domain equals one.

There is no scientific evidence to support EPA's selection of these "critical metrics" as being more important than other metrics, i.e., why within the "study participation" domain "selection" and "attrition" are more important than "comparison group"; and there are no data supporting EPA's choice of particular numbers for weighting these 'critical metrics' (i.e., some metrics are "twice" as important as the other metrics).

Overall, there is no scientific justification for EPA to assign these or any other quantitative scoring measures for assessing the quality of an individual study. The implicit assumption in quantitative scoring methods is that we know empirically how much each risk of bias domain contributes to study quality, and that these domains are independent of each other. This is not a scientifically supportable underlying assumption. Research has documented that scoring methods have, at best, unknown validity, may contain invalid items, and that results of a quality score are not scientifically meaningful or predictive of the quality of studies (26-28). An examination of the application of quality scores in meta-analysis found that quality-score weighting produced biased effect estimates, with the authors explaining that quality is not a singular dimension that is additive, but that it is possibly non-additive and non-linear (29).

Aggregating across quality criteria to produce a single score is recognized by preeminent systematic review methodologists as problematic and unreliable because the weights assigned are arbitrary and focus on the quality of reporting rather than the design and conduct of the research (21, 30). Scoring is not utilized by empirically based systematic review methodologies, such as the Cochrane Collaboration or GRADE (21, 31). As stated by the Institute of Medicine, "... systematic review teams have moved away from scoring systems to assess the quality of individual studies toward a focus on the components of quality and risk of bias" (16).

The Cochrane Collaboration, founded in 1993, is an international non-profit and independent organization that produces and disseminates systematic reviews of healthcare interventions and is a key locus of the world's most authoritative expertise on systematic review methods. Cochrane's methodology states: "The current standard in evaluation of clinical research calls for reporting each component of the assessment tool separately **and not calculating an overall numeric score (emphasis added)**"(31).

The National Academy of Sciences in its review of the EPA's IRIS program's method for SR, strongly supported a methodology that did not incorporate quantitative scoring, stating:

... Cochrane discourages using a numerical scale because calculating a score involves choosing a weighting for the subcomponents, and such scaling generally is nearly impossible to justify (Juni et al. 1999). Furthermore, a study might be well designed to eliminate bias, but because the study failed to report details in the publication under review, it will receive a low score. Most scoring systems mix criteria that assess risk of bias and reporting. However, there is no empirical basis for weighting the different criteria in the scores. Reliability and validity of the scores often are not measured. Furthermore, quality scores have been shown to be invalid for assessing risk of bias in clinical research (Juni et al. 1999). The current standard in evaluation of clinical research calls for reporting each component of the assessment tool separately and not calculating an overall numeric score (Higgins and Green 2008) (17)(Pg. 69).

b) EPA's scoring method wrongly conflates how well a study is reported with how well the underlying research was conducted.

Study reporting addresses how well research findings are written up, i.e., whether there is a complete and transparent description of what was planned, what was done, what was found, and what the results mean. Guidelines and checklists for authors have been developed to help ensure all information pertinent to assessing the quality and meaning of research is included in the report. The "Strengthening of Reporting of Observational Studies in Epidemiology" or "STROBE" Initiative is an example of a checklist of items that should be included in articles reporting such research.¹

EPA's SR Framework uses reporting measures in its scoring of the quality of human studies, including incorporating reporting guidelines into the reasons for scoring studies "low quality" (Metrics 1 and 15) or "unacceptable for use" (Metrics 2, 3, 4, 6, 7). EPA's SR Framework acknowledges that reporting is not the same as an underlying flaw in study methodology (Pg. 31), but then proceeds to ignore this distinction by using reporting as a measure of the quality of the underlying research. EPA's SR Framework not only does not "untangle" reporting from quality, it specifically conflates the two by using metrics in the STROBE reporting guidelines to score individual studies. The authors of the STROBE guidelines specifically note the guidelines are not a measure of the quality of the underlying research, stating:

The STROBE Statement is a checklist of items that should be addressed in articles reporting on the 3 main study designs of analytical epidemiology: cohort, case control, and cross-sectional studies. The intention is solely to provide guidance on how to report observational research well; these recommendations are not prescriptions for designing or conducting studies. Also, while clarity of reporting is a prerequisite to evaluation, the checklist is not an instrument to evaluate the quality of observational research (emphasis added). ... Our intention is to explain how to report research well, not how research should be done. We offer a detailed explanation for each checklist item. Each explanation is preceded by an example of what we consider transparent reporting. This does not mean that the study from which the example was taken was uniformly well reported or well done; nor does it mean that its findings were reliable, in the sense that they were later confirmed by others: it only means that this particular item was well reported in that study."(32)

How completely and clearly a study is reported is not a scientifically valid measure of the quality of the

¹ See Strobe statement at: <https://www.strobe-statement.org/index.php?id=strobe-aims>

underlying research (20, 21, 33, 34). As GRADE methodologists have succinctly stated, “... just because a safeguard against bias is not reported does not mean it was neglected”(21). Moreover, including many reporting items that are irrelevant to bias in a quality scoring rule (e.g., an indicator of whether power calculations were reported), will disproportionately reduce some of the resulting scores (29).

The Cochrane Collaboration Handbook for conducting a SR clearly distinguishes reporting and bias, the latter which is defined as “a systematic error, or deviation from the truth, in results or inferences” (20). The Cochrane Manual for conducting systematic reviews is explicit about not conflating reporting with bias, stating:

Bias may be distinguished from **quality**. The phrase ‘assessment of methodological quality’ has been used extensively in the context of systematic review methods to refer to the critical appraisal of included studies. The term suggests an investigation of the extent to which study authors conducted their research to the highest possible standards. This *Handbook* draws a distinction between assessment of methodological quality and assessment of risk of bias, and recommends a focus on the latter. The reasons for this distinction include:

1. The key consideration in a Cochrane review is the extent to which results of included studies should be *believed*. Assessing risk of bias targets this question squarely.
2. A study may be performed to the highest possible standards yet still have an important risk of bias. For example, in many situations it is impractical or impossible to blind participants or study personnel to intervention group. It is inappropriately judgemental to describe all such studies as of ‘low quality’, but that does not mean they are free of bias resulting from knowledge of intervention status.
3. Some markers of quality in medical research, such as obtaining ethical approval, performing a sample size calculation and reporting a study in line with the CONSORT Statement (Moher 2001d), are unlikely to have direct implications for risk of bias.
4. An emphasis on risk of bias overcomes ambiguity between the quality of reporting and the quality of the underlying research (although does not overcome the problem of having to rely on reports to assess the underlying research).

Importantly, in the application of EPA’s SR Framework, studies can be scored as “low quality,” and even excluded from EPA’s review, based solely on a deficiency in reporting, irrespective of the quality of the underlying research. Research documents that important information is often missing or unclear in published research (35), as word limits, styles, and other specifications are highly variable, and non-standardized among peer-reviewed journals. As such, efforts to improve reporting are focused on uptake of reporting guidelines by journal editors and researchers (32, 36, 37). Improving reporting is needed in academic research, but as stated by the developers of the STROBE guidelines, “We want to provide guidance on how to report observational research well. ... the checklist is not an instrument to evaluate the quality of observational research.”

Given the historical and present-day deficiencies in how studies are reported in the peer-reviewed literature, and because EPA’s scoring system rates as ‘unacceptable for use’ any human study that does not report even one of five reporting metrics, EPA’s proposal could reasonably be expected to lead to the exclusion from EPA’s consideration much of the existing body of knowledge on the impact of

environmental chemicals on human health, and is inconsistent with TSCA mandates to use the “best available science” and “reasonably available information.”^m Applying flawed exclusion criteria that directly contradicts widely accepted empirically based SR methodological approaches will almost certainly result in flawed conclusions and threaten the protection of the public’s health.

(c) EPA’s scoring method excludes research based on one single reporting or methodological limitation.

In the “fatal flaw” component of EPA’s SR Framework’s scoring system, for each type of evidence stream, i.e., epidemiologic, animal, *in vitro*, etc., EPA created an arbitrary list of metrics that make studies “unacceptable for use in the hazard assessment,” stating:

EPA/OPPT plans to use data with an overall quality level of *High, Medium, or Low* confidence to quantitatively or qualitatively support the risk evaluations, but does not plan to use data rated as *Unacceptable*. Studies with any single metric scored as 4 will be automatically assigned an overall quality score of *Unacceptable* and further evaluation of the remaining metrics is not necessary (emphasis added). An *Unacceptable* score means that serious flaws are noted in the domain metric that consequently make the data unusable (or invalid) (Pg. 227).

There is no empirical basis for EPA’s selected list of fatal flaws.

Illustrative of this “fatal flaw” aspect of EPA’s scoring system, for human epidemiologic studies (See Section H.5, Table H-8 (page 231), EPA lists six domains of study quality, i.e., study participation; exposure characterization; outcome assessment; potential confounding/variable control; analysis; and other considerations for biomarker selection and measurement, and 19 metrics to assess the six domains. A study that has even one of the 19 “serious flaws” metrics is considered to be “unacceptable for use.”

The underlying assumptions of EPA’s “serious flaws” metrics are not science-based because:

- **EPA's list of "serious flaws" are not all equal indicators of study quality:**
For example, among human observational studies, any one of the list of 19 metrics can eliminate a study from consideration as EPA considers all of these "flaws" to be of equal import; as described in detail above, such weighting is arbitrary and not a science-based method.
- **EPA's list of "serious flaws" are not all related to real flaws in the underlying research:**
 - **Reporting** guidelines are wrongly equated with “serious flaws” in study quality.
For example, in scoring the quality of human studies, 5 of 19 “serious flaw” metrics (Table H-8) are STROBE reporting guidelines (STROBE checklist items # 6,7,8,13,15). A study would be scored as “unacceptable for use” by EPA based on any one of these STROBE reporting guidelines. As described above in comment #2a, the STROBE guideline developers explicitly state this is neither the intended nor a scientifically valid use of these guidelines. (32)

^m 15 USC §2625(h) and (k)

- **Analysisⁿ** is equated with a "serious flaw" in study quality, but statistical power^o alone is not a valid measure of study quality. For example, EPA's framework excludes human studies that do not meet EPA's criteria for "high" in the analysis domain. EPA does not state how it will calculate whether a study is "adequately" powered. According to EPA's framework, to be included in an EPA review, a study must meet the "high" criteria in EPA's "Metric 13, Statistical power (sensitivity, reporting bias)" as presented in the box below. Studies that are not "high" quality for this metric would be designated as "unacceptable for use" by EPA:

Metric 13. Statistical power (sensitivity, reporting bias)
Instructions: To meet criteria for confidence ratings for metrics where 'AND' is included, studies must address both of the conditions where "AND" is stipulated. To meet criteria for confidence ratings for metrics where 'OR' is included studies must address at least one of the conditions stipulated.

EPA Metric 13. Excerpted from Table H-9 (page 243)

High (score = 1)	<p><u>For cohort and cross-sectional studies:</u> The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population.</p> <p>OR</p> <p>The paper reported statistical power high enough ($\geq 80\%$) to detect an effect in the exposure population and/or subgroups of the total population.</p> <p><u>For case-control studies:</u> The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population.</p> <p>OR</p> <p>The paper reported statistical power was high ($\geq 80\%$) to detect an effect in the exposure population and/or subgroups of the total population.</p>
Medium (score = 2)	<ul style="list-style-type: none"> • Do not select for this metric.
Low (score = 3)	<ul style="list-style-type: none"> • Do not select for this metric.
Unacceptable (score = 4)	<ul style="list-style-type: none"> • <u>For cohort and cross-sectional studies:</u> The number of participants are inadequate to detect an effect in the exposed population and/or subgroups of the total population. • <u>For case-control studies:</u> The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population.

ⁿ See Table H-8 "Serious Flaws that Would Make Epidemiological Studies Unacceptable for Use in the Hazard Assessment" under the "analysis domain" "statistical power/sensitivity" metric (page 233) "in conjunction with Table H-9 "Evaluation Criteria for Epidemiologic Studies, Metric 13 "statistical power (sensitivity, reporting bias) (page 243).

^o A power calculation is an estimate of the size of the study population needed to detect an effect of a given size.

First and foremost, EPA provides no method for how it will determine the “adequacy” of the statistical power of a study on which to base its score, and provides no rationale for excluding studies with less than 80% statistical power. According to STROBE guideline developers, ... “before a study is conducted power calculations are made with many assumptions that once a study is underway may be upended; further, power calculations are most often not reported” (32).

EPA’s Metric 13 statistical power/sensitivity also appears to confuse bias with imprecision. Individual studies that are “underpowered” (for example, because in the real world the exposed population may not be large enough for statistical purposes even if they are health impacted) can still be potentially valuable to science-based decision-making. For example a small study may be imprecise but that should not be confused with whether it is biased (20); a small study can be imprecise but at the same time less biased than a larger study (17). Small “underpowered” studies can also be combined in a meta-analysis that increases the statistical power of the body of evidence to reflect the relationship between an exposure and a health impact. Additionally, “underpowered” studies that find a health effect to be present may be indicative of a larger effect size than anticipated. Thus, omitting such studies would severely bias the conclusions of the review.

Illustrative of how EPA’s “analysis” metric could result in excluding high quality research that can inform science-based decision-making by EPA, in a 2017 systematic review by Lam et al. “*Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis*,” (12) none of the 4 high-quality^p studies included in the meta-analysis reported a power calculation, and yet together, these studies found “a 10-fold increase (in other words, times 10) in PBDE exposure associated with a decrement of 3.70 IQ points (95% confidence interval:0.83,6.56).” It is also notable that one of the studies in the meta-analysis, Herbstman et al. 2010, (38) was assessed by the review authors to be “probably high risk of bias” for “Incomplete Outcome Data.”^q As such, this otherwise high quality study, i.e., all of the other domains were “definitely” or “probably” low risk of bias, would meet EPA’s criteria for “unacceptable for use” based on STROBE reporting guideline #15, “Report numbers of outcome events or summary measures over time”.^r

In short, the *Lam et al* systematic review, using the best available scientific methods, found that a ubiquitous environmental contaminant is impacting human intelligence, a finding that was subsequently reviewed and endorsed by the National Academy of Sciences (19). Yet EPA’s SR review framework would exclude crucial pieces of this body of evidence based on the Agency’s inaccurate, non-science-based criteria for deeming studies ‘unacceptable.’ This is contrary to TSCA’s mandate to use the best available science.^s

- **"Level of exposure" is equated with a "serious flaw".**

^p “High quality” defined as “definitely” or “probably” low or very low risk of bias (Figure 2a in the *Lam et al* paper) based on specific and detailed definitions of risk of bias established before the review was conducted.

^q The authors of the systematic review rated the Herbstman 2010 study “probably high risk of bias” for “incomplete outcome data” based on the following rationale: “Concerns regarding missing outcome data at each follow-up time on almost half the cohort of 210 with cord blood PBDE measurements; no argument is presented that would invalidate the possibility of a selection bias (i.e., likelihood that outcome data is missing is related both to outcome status and exposure).”

^r See Table H-8 “Serious Flaws that Would Make Epidemiological Studies Unacceptable for Use in the Hazard Assessment” under the “outcome assessment domain” “Outcome measurement or characterization” metric (page 232) which specified STROBE guideline #15 to assess this metric.

^s 15 USC §2625 (h)

EPA's "exposure characterization" domain for human studies includes the level of exposure as a fatal flaw, stating: "For all study types: The **levels** of exposure are not sufficient or adequate (as defined above)^t to detect an effect of exposure (Cooper et al., 2016)." Unlike human experimental studies, which are largely precluded for ethical reasons, human observational studies can only be based on what exposures actually occur in the real world. EPA offers no explanation of how one could know whether the levels would be "sufficient or adequate" enough to detect an effect. Given the vagaries of this metric, it could be reasonably anticipated that it would permit EPA to arbitrarily exclude quality research from its decision-making.

We recommend: EPA should not use a quantitative scoring method to assess quality in individual studies; it should not conflate study reporting with study quality; and it should not exclude otherwise quality research based on a single reporting or methodological limitation. Rather EPA should employ a scientifically valid method to assess risk of bias of individual studies.

^t EPA "as defined above" is unclear, presumably "as defined above" refers to the definition of the domain in Table H-2 page 223, "Evaluation of exposure assessment methodology that includes consideration of methodological quality, sensitivity, and validation of the methods used, degree of variation in participants, and an established time order between exposure and outcome."

3. EPA's TSCA systematic review framework does not consider financial conflicts of interest as a potential source of bias in research.

As observed by the Deputy Editor (West) of JAMA in 2010, "the biggest threat to [scientific] integrity [is] financial conflicts of interest" (39). Yet EPA's systematic review framework is silent on how it will take into account this empirically documented influence on the results of scientific research. Underscoring this EPA SR framework deficiency is the fact that recent studies empirically document that industry sponsorship produces research that is favorable to the sponsor (40, 41). The influence of financial ties on research can be traced to a variety of types of biases, and this conflict of interest needs to be distinguished from non-financial interests in the research, which can also affect research (42).

The fact that funding source needs to be accounted for in some manner is empirically supported and not a subject of scientific debate; what scientists differ on is *how* to best address funding as a potential source of bias (43, 44); for example, whether funding source is assessed as a specific risk of bias domain (43) or considered at multiple points in the evaluation (20, 44). For example, funding source is recommended as a factor to consider when evaluating risk of bias of individual studies for selective reporting, and then again for evaluating the body of evidence for publication bias, (45) and/or to be considered as a potential factor to explain apparent inconsistency within a body of evidence (14).

A 2017 Cochrane systematic review of industry sponsorship and research outcome concluded ... "industry sponsorship should be treated as bias-inducing and industry bias should be treated as a separate domain" (40). The National Academy of Sciences in its review of the EPA IRIS program's SR method found that "Funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS assessment (17)(p 79).

Notably, EPA's exclusion of consideration of funding source and other potential conflicts of interests is also internally inconsistent with EPA's own improper reliance on STROBE guidelines as quality measures: STROBE guidelines item #22 specified that "the source of funding and the role of funders, could be addressed in an appendix or in the methods section of the article" (32).

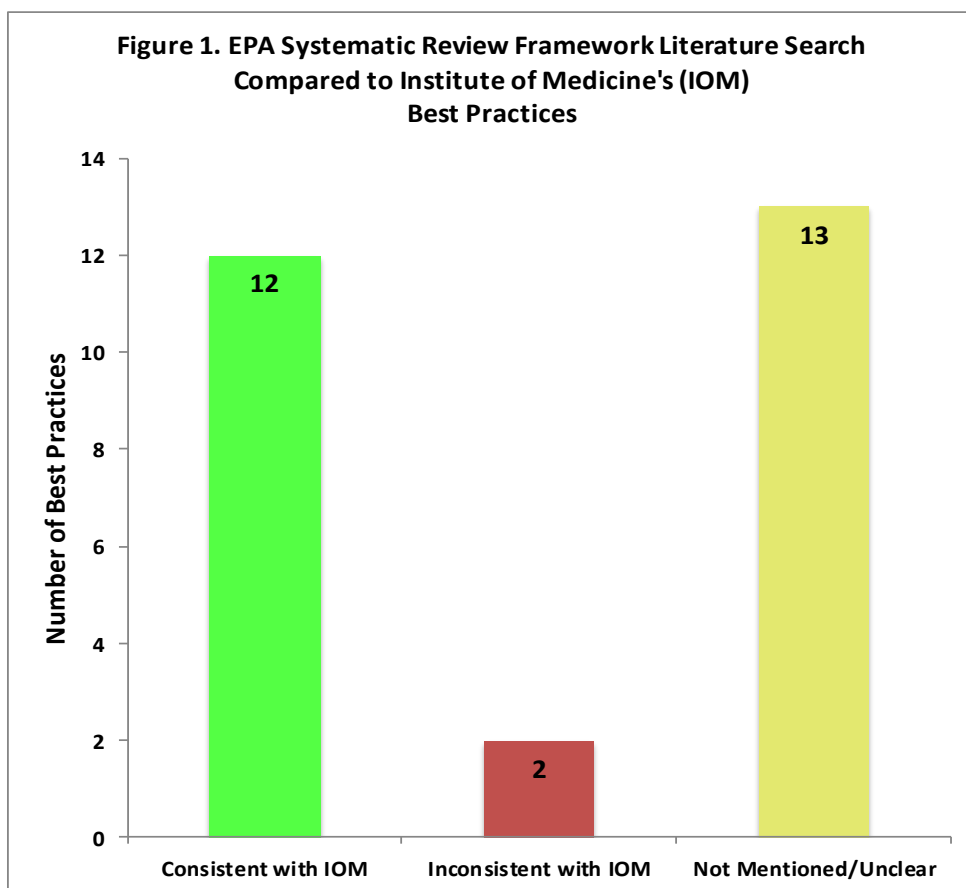
Importantly, including funding as a risk of bias as a domain does not mean excluding industry sponsored studies from EPA's hazard and risk assessment; it only means documenting funding as one of many domains of potential bias and evaluating its impact on the overall quality of the body of evidence.

We recommend: EPA should assess study and author funding source as a risk of bias domain for individual studies.

4. The literature review step of EPA’s TSCA systematic review framework incorporates select best practices, but also falls short of, or is unclear about, many other best practices for conducting a systematic and transparent literature review.

Overall, we commend the EPA for its efforts to incorporate many best practices for a comprehensive literature search in its systematic review framework. We compared EPA’s framework for systematic review to the Institute of Medicine’s (IOM’s) best practices for the literature review step of a systematic review (16)(See IOM 2011 Chapter 3. and TABLE E-1), which was applied by the National Academy of Sciences in its review of EPA’s IRIS Program methods for systematic review (17)(See Table 4-1 Pp. 43-55).

We found EPA’s framework to be consistent with 12 of IOM’s 27 best practices for conducting a literature search (Figure 1 and Appendix 1). There are two key features of EPA’s framework that are clearly inconsistent with IOM’s best practices. EPA fails: (1) to include or exclude studies based on the protocol’s pre-specified criteria, a practice that is critical to avoiding results-based decisions;^u and (2) to use two or more members of the review team, working independently, to screen and select studies, which is an essential quality-assurance measure.^v



^u See our Comment #1 regarding the EPA framework’s lack of a pre-defined protocol.

^v EPA’s framework, “Summary of the Title/Abstract Screening Conducted for the First Ten TSCA Risk Evaluations” (page 24) states that only one screener conducted the screening and categorization of titles and abstracts.

For the remaining 13 IOM best practices, EPA's framework is either unclearly stated (N=7) or the practice is not mentioned at all (N=6). However, based on the literature review methods presented in the First Ten TSCA Risk Evaluations, EPA's framework appears to have incorporated six additional best practices that are either unclear or not mentioned in EPA's SR framework: (1) work with a librarian or other information specialist trained in performing systematic reviews to plan the search strategy (IOM 3.1.1); (2) Design the search strategy to address each key research question (IOM 3.1.2); (3) Search regional bibliographic databases if other databases are unlikely to provide all relevant evidence (IOM 3.1.9); (4) Conduct a web search (IOM 3.2.5); and (5) Provide a line-by-line description of the search strategy, including the date of search for each database, web browser, etc. (IOM 3.4.1).

EPA should make its framework for conducting a literature review transparently congruent with all of IOM's best practices. This includes addressing two critical inconsistencies: (1) include or exclude studies based on the protocol's pre-specified criteria to prevent results-based decisions; and (2) Use two or more members of the review team, working independently, to screen and select studies, to ensure quality assurance. The transparency of the framework would be improved by specifying how EPA is addressing each best practice; at this juncture, how EPA intends to specifically handle many components of its literature searches could not readily be identified.

For example, the framework is unclear about whether EPA will include papers published in languages other than English. The exclusive reliance on English-language studies may lead to under-representation of the entire body of available evidence, and studies have also suggested that language bias might lead to erroneous conclusions (46). Furthermore, when considering the inclusion or update of an existing systematic review, studies have found that language-inclusive systematic reviews (including studies in languages other than English) were of the highest quality, compared with other types of reviews (47). Online translation tools are readily available to allow screeners to quickly evaluate study abstracts for relevance, and therefore we recommend EPA to incorporate non-English language studies in their screening and not simply exclude in advance these potentially relevant papers.

Additionally, EPA's framework should explicitly include rules for determining when the list of relevant studies will be considered final i.e., "stopping rules." Newer scientific studies will inevitably continue to appear in scientific journals and it will be impossible to continually attempt to include all these studies in a chemical assessment. To meet the deadlines as mandated by the Lautenberg Amendments, EPA should state clear stopping rules in the form of deadlines or criteria for when the body of included relevant studies will be finalized for the purposes of the chemicals assessment. We also strongly encourage EPA in its stated exploration of automation and machine learning tools,^w which can help speed the production of EPA's systematic reviews.

We recommend: EPA should make its framework for conducting a literature review congruent with all of the Institute of Medicine's best practices, and explicitly include rules for when the list of relevant studies will be considered final.

^w Footnote 9 page 23 states "In addition to using DistillerSR, EPA/OPPT is exploring automation and machine learning tools for data screening and prioritization activities (e.g., SWIFT-Review, SWIFT-Active Screener, Dragon, DocTER). SWIFT is an acronym for "Sciome Workbench for Interactive Computer-Facilitated Text-mining".

5. EPA's TSCA systematic review framework correctly recognizes that mechanistic data are not required for a hazard assessment, but EPA is not clear that these data, if available, can only be used to increase, and not to decrease, confidence in a body of evidence.

EPA's TSCA framework (page 172) states that EPA will use the evaluation strategies for animal and *in vitro* toxicity data to assess the quality of mechanistic and pharmacokinetic data supporting the model, and may tailor its criteria further to evaluate new approach methodologies (NAMs). We agree with EPA that mechanistic data need to be evaluated in a manner comparable to how other streams of evidence are evaluated. Data generated by alternative test methods (such as high-throughput screening methods) are not different than any other type of *in vitro* or cell-based assay data that would be considered in a systematic review. These kinds of assays provide mechanistic data. However, in this case, as described in comment # 2 above, EPA's use of its evaluation strategies for animal and *in vitro* toxicity data would entail using a quantitative scoring method that is incompatible with the best available science in fundamental ways. EPA should employ a scientifically valid method to assess risk of bias of individual studies in *all* streams of evidence, including mechanistic data.

EPA's framework (page 172) states, "the availability of a fully elucidated mode of action (MOA) or adverse outcome pathway (AOP) is not required to conduct the human health hazard assessment for a given chemical (emphasis added)." We strongly agree with EPA that mechanistic data are not needed for a hazard assessment. In addition, EPA's framework should be explicit that mechanistic data are only used to increase confidence in a hazard assessment, and never to decrease confidence.

The National Academy of Sciences explicitly considered how mechanistic data could be utilized in a systematic review for evidence integration (19). The committee came to two conclusions. First, the same protocol for evaluating relevance and study quality must be used with mechanistic data as for any other study. For example, in the report's case study on phthalates, the committee was not able to integrate results from high-throughput assays because the cell lines used were of unknown relevance to the *in vivo* mechanism of phthalate toxicity (19)(pg.78). Second, the foundation of the hazard classification in a systematic review is the animal and human data, with the mechanistic data playing a supporting role. If mechanistic data is relevant, it can be used to upgrade a hazard classification, or increase the confidence of a finding made based on evaluation of animal and human data. A hazard classification is never made based on high-throughput or other kinds of mechanistic data alone (19)(Pp. 158-9).

We recommend: EPA should be explicit that mechanistic data can only be used to upgrade a hazard classification, or increase the confidence of a finding made based on evaluation of animal and human data, and that these data will not be used to decrease confidence in a body of evidence.

6. EPA's TSCA systematic review framework is not independent of the regulatory end user of the review.

EPA's TSCA systematic review/risk assessment process is not independent of the TSCA risk management process, a conflict that is incompatible with best scientific methods. EPA's SR framework was developed and is being implemented by the Office of Chemical Safety and Pollution Prevention (OCSPP), which is also responsible for regulating the environmental exposures under TSCA review. In contrast, other EPA chemical assessment programs such as the IRIS program are intentionally placed in a non-regulatory research arm (the Office of Research and Development), to create separation from the Agency's program office responsible for regulatory decisions. This separation supports IRIS's ability to develop impartial chemical toxicity information independent of its ultimate use by EPA's program and regional office in risk assessment and risk management decisions. The National Academy of Sciences supported this in its 2018 report, stating that: "Current best practices [for systematic reviews in other medical disciplines] recommended by the Institute of Medicine (IOM 2011) suggest that the IRIS teams involved in the systematic-review process **should be independent of those involved in regulatory decision-making** who use the products of the systematic-review teams (**emphasis added**)" (15). This same principle should also be implemented across the Agency and specifically for TSCA assessments.

We recommend: EPA's systematic reviews should be produced independently of the regulatory end user of the review.

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Appendix 1: Comparison of IOM literature review best practices with EPA systematic review framework

IOM Standard (IOM 2011) and Rationale as cited in 2014 National Academy Review of the IRIS program (pp 43-55)	EPA Systematic Review Framework	Consistent with IOM	Inconsistent with IOM	Not Mentioned	Unclear	Apparently applied to first 10 chemicals
3.1 Conduct a comprehensive systematic search for evidence						
3.1.1 Work with a librarian or other information specialist trained in performing systematic reviews to plan the search strategy (p. 266). Rationale: As with other aspects of research, specific skills and training are required to navigate a wide range of bibliographic databases and electronic information sources.	<p><u>Not mentioned in the EPA Systematic Review Framework; based on first 10 chemicals EPA Systematic Review Framework consistent with this best practice.</u></p> <p>Table 3-2 page 29 provides web links to the Strategy for Conducting Literature Searches and Bibliography documents published in June 2017 along with each of the first ten TSCA Scope documents. Within these documents it states that a professional librarian developed the search.</p>			1		1
3.1.2 Design the search strategy to address each key research question (p. 266). Rationale: The goal of the search strategy is to maximize both sensitivity (the proportion of all eligible articles that are correctly identified) and precision (the proportion of all articles identified by the search that are eligible). With multiple research questions, a single search strategy is unlikely to cover all questions posed with any precision.	<p><u>Unclear in the EPA Systematic Review Framework; based on first 10 chemicals EPA Systematic Review Framework consistent with this best practice.</u></p> <p>Table 3-2 page 29 provides web links to the Strategy for Conducting Literature Searches and Bibliography documents published in June 2017 along with each of the first ten TSCA Scope documents. Within these documents multiple search strategies are presented.</p>				1	1
3.1.3 Use an independent librarian or other information specialist to peer review the search strategy (p. 267). Rationale: This part of the evidence review requires peer review like any other part. Given the specialized skills required, a person with similar skills would be expected to serve as peer reviewer.	<u>Not mentioned in the EPA Systematic Review Framework;</u>			1		
3.1.4 Search bibliographic databases (p. 267). Rationale: A single database is typically not sufficient to cover all publications (journals, books, monographs, government reports, and others) for clinical research. Databases for reports published in languages other than English and for the gray literature could also be searched.	<p>EPA Systematic Review Framework is consistent with this best practice.</p> <p>pp 21-22 EPA SR Framework - "EPA/OPPT designed its initial data search to be broad enough to capture a comprehensive set of sources containing data/information potentially relevant to the risk evaluation process. Generally, the search was conducted on a wide range of data/information sources, includingbut not limited to peer-reviewed and grey literature8. When available, EPA/OPPT relied on the search strategies from recent assessments (e.g., EPA Integrated Risk Information System (IRIS) assessments) as a starting point to identify relevant references and supplemented these searches to identify relevant information published after the end date of the previous search to capture more recent literature." "Following the initial search of data for the first ten risk evaluations, EPA/OPPT searched for data submitted to EPA under TSCA sections 4, 5, 8(e), and 8(d), as well as for your information (FYI) submissions, to find additional data relevant to human health and environmental hazard, exposure, fate, engineering, physical-chemical properties, and TSCA conditions of use."</p>	1				
3.1.5 Search citation indexes (p. 267). Rationale: Citation indexes are a good way to ensure that eligible reports were not missed.	<p>EPA Systematic Review Framework is consistent with this best practice.</p> <p>EPA is searching Web of Science, a citation index, which searches Science, Social Science, and Arts & Humanities citation indexes</p>	1				

3.1.6 Search literature cited by eligible studies (p. 268). Rationale: The literature cited by eligible studies (for example, references provided in a journal article or thesis) is a good way to ensure eligible reports were not missed.	<p>EPA Systematic Review Framework is consistent with this best practice.</p> <p>EPA/OPPT identified additional environmental fate and exposure references that were not captured in the initial categorization of the on-topic references for the first ten risk evaluations published on June 22, 2017. Specifically, assessors identified references <u>by checking the list of references of data sources frequently used to support EPA/OPPT's risk assessments (e.g., previous assessments cited in Table 1-1 of the TSCA Scope documents)</u>. This method, called backward reference searching (or snowballing), was not part of the initial literature search strategy. The inclusion of these additional on-topic references is not expected to change the information presented in the TSCA Scope and Problem Formulation documents. Also, EPA/OPPT anticipates targeted supplemental searches during the analysis phase (e.g., to locate specific information for exposure modeling). Backward reference searching will be included in the literature search strategy for supplemental searches.</p>	1				
3.1.7 Update the search at intervals appropriate to the pace of generation of new information for the research question being addressed (p. 268). Rationale: Given that new articles and reports are being generated in an ongoing manner, searches would be updated regularly to reflect new information relevant to the topic.	<p><u>Not mentioned in the EPA Systematic Review Framework;</u></p>	1				
3.1.8 Search subject specific databases if other databases are unlikely to provide all relevant evidence (p. 268). Rationale: If other databases are unlikely to be comprehensive, search a variety of other sources to cover the missing areas.	<p><u>EPA Systematic Review Framework is consistent with this best practice.</u></p> <p>The databases searched are not named in the EPA Systematic Review Framework. However, Table 3-2 page 29 provides web links to the Strategy for Conducting Literature Searches and Bibliography documents published in June 2017 along with each of the first ten TSCA Scope documents. Within these documents subject specific databases are searched.</p> <p>pp 21-22 "EPA/OPPT designed its initial data search to be broad enough to capture a comprehensive set of sources containing data/information potentially relevant to the risk evaluation process. Generally, the search was conducted on a wide range of data/information sources, including but not limited to peer-reviewed and grey literature⁸. When available, EPA/OPPT relied on the search strategies from recent assessments (e.g., EPA Integrated Risk Information System (IRIS) assessments) as a starting point to identify relevant references and supplemented these searches to identify relevant information published after the end date of the previous search to capture more recent literature. For human health hazards, the literature search strategy was designed to identify relevant data/information in favor (e.g., positive study) or against (e.g., negative study) a given hypothesis within the context of the assessment question(s) being evaluated in the risk evaluation." "Following the initial search of data for the first ten risk evaluations, EPA/OPPT searched for data submitted to EPA under TSCA sections 4, 5, 8(e), and 8(d), as well as for your information (FYI) submissions, to find additional data relevant to human health and environmental hazard, exposure, fate, engineering, physical-chemical properties, and TSCA conditions of use. Searches were conducted of CBI and non-CBI databases followed by a duplicate identification step. Many of the non-CBI data submissions were captured in the initial search published on June 22, 2017, but some were found and added to the pool of new references to undergo data screening."</p>	1				
3.1.9 Search regional bibliographic databases if other databases are unlikely to provide all relevant evidence (p. 269). Rationale: Many countries have their own databases and either because of language or other regional factors the reports are not necessarily also present in US-based databases	<p><u>Unclear in the EPA Systematic Review Framework; based on first 10 chemicals EPA Systematic Review Framework consistent with this best practice in that state databases are searched.</u></p>	1	1			

3.2 Take action to address potentially biased reporting of research results

3.2.1 Search gray literature databases, clinical trial registries, and other sources of unpublished information about studies (p. 269). Rationale: Negative or null results, or undesirable results, might be published in difficult to access sources.	<u>EPA Systematic Review Framework is consistent with this best practice.</u> p 21-22 "Generally, the search was conducted on a wide range of data/information sources, <u>including but not limited to peer-reviewed and grey literature</u> "	1				
3.2.2 Invite researchers to clarify information about study eligibility, study characteristics, and risk of bias (p. 269). Rationale: Rather than classify identified studies as missing critical information, it is preferable to ask the investigators directly for the information.	<u>EPA Systematic Review Framework is consistent with this best practice.</u> age 26 "When applicable and feasible, EPA/OPPT <u>will reach out to the authors of the data/information source to obtain raw data or missing elements that would be important to support the data evaluation and data integration steps.</u> In such cases, the request(s) for additional data/information, number of contact attempts, and responses from the authors will be documented."	1				
3.2.3 Invite all study sponsors and researchers to submit unpublished data, including unreported outcomes, for possible inclusion in the systematic review (p. 270). Rationale: So as to include all relevant studies and data in the review, ask sponsors and researchers for information about unpublished studies or data.	<u>Not mentioned in the EPA Systematic Review Framework;</u>		1			
3.2.4 Hand search selected journals and conference abstracts (p. 270). Rationale: Hand searching of sources most likely provides relevant up-to-date information and contributes to the likelihood of comprehensive identification of eligible studies.	<u>Not mentioned in the EPA Systematic Review Framework;</u>		1			
3.2.5 Conduct a web search (p. 271). Rationale: Web searches, even when broad and relatively untargeted, can contribute to the likelihood that all eligible studies have been identified.	<u>Unclear in the EPA Systematic Review Framework; based on first 10 chemicals EPA Systematic Review Framework consistent with this best practice.</u>		1			1
3.2.6 Search for studies reported in languages other than English if appropriate (p. 271). Rationale: There is limited evidence that negative, null, or undesirable findings might be published in languages other than English.	<u>Not mentioned in EPA Systematic Review Framework; unclear in first 10 chemicals EPA Systematic Review, for example ecotox on methylene chloride excludes non english papers</u>		1			

3.3 Screen and select studies

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3.3.1 Include or exclude studies based on the protocol's pre-specified criteria (p. 272). Rationale: On the basis of the study question, inclusion and exclusion criteria for the review would be set a priori, before reviewing the search results (see 3.3.5) so as to avoid results-based decisions.

EPA Systematic Review Framework is inconsistent with this best practice; no pre-specified protocols developed for the first 10 chemicals; criteria listed in chemical specific strategies for conducting literature searches lack specificity needed to rapidly and transparently screen relevant papers. Figure 3-1 includes protocol development as a first step. However, Table 3-1 begins with the data search phase of EPA's systematic review method. On page 19 EPA states, "The timeframe for development of the TSCA Scope documents has been very compressed. ... EPA had limited ability to develop a protocol document detailing the systematic review approaches and/or methods prior to the initiation of the risk evaluation process for the first ten chemical substances. For these reasons, the protocol development is staged in phases while conducting the assessment work." EPA's application of inclusion/exclusion criteria for the first 10 chemicals (based on asbestos and methylene chloride) only generally lists inclusion and exclusion criteria. Methylene chloride: page 80 INCLUDE: Studies evaluating human health effects resulting from exposure to the chemical. Includes epidemiology studies (measure an adverse outcome in an exposed population), experimental studies (e.g. individuals exposed to chemical in a controlled study) and case studies (e.g. individual case report on accidental exposure to chemical) ☐ Acute, subchronic, and chronic exposures
**Also choose applicable health effect tags in next section "Methylene Chloride (DCM) Health Effect Tags"
EXCLUDE: Occupational studies that do not specify specific solvent exposure
page 83 asbestos - INCLUDE: Studies evaluating human health effects resulting from exposure to the chemical. Includes epidemiology studies (measure an adverse outcome in an exposed population), experimental studies (e.g. individuals exposed to chemical in a controlled study) and case studies (e.g. individual case report on accidental exposure to chemical) Acute, subchronic, and chronic exposures
**Also choose applicable health effect tags in next section "asbestos Health Effect Tags"

1

3.3.2 Use observational studies in addition to randomized controlled trials to evaluate harms of interventions (p. 272). Rationale: Predetermine study designs that will be eligible for each study question.

EPA Systematic Review Framework is consistent with this best practice.

1

3.3.3 Use two or more members of the review team, working independently, to screen and select studies (p. 273). Rationale: Because reporting is often not clear or logically placed, having two independent reviewers is a quality-assurance approach.

EPA Systematic Review Framework is not consistent with this best practice. Based on first 10 chemicals EPA Systematic Review Framework one reviewer was used for title and abstract screening.

1

Section 3.2.2.1 Title and abstract screening - page 23. "Each article is generally screened by two independent reviewers using specialized web-based software (i.e., DistillerSR)⁹. Screeners are assigned batches of references after conducting pilot testing. Screening forms are typically used to facilitate the screening process by asking a series of questions based on pre-determined inclusion and exclusion criteria. The screeners resolve conflicts by consensus, or consultation with an independent individual(s)."

p. 24 "3.2.2.1.1 Summary of the Title/Abstract Screening Conducted for the First Ten TSCA Risk Evaluations
One screener (11) conducted the screening and categorization of titles and abstracts. Relevant studies were identified according to inclusion and exclusion criteria as described in the Strategy for Conducting Literature Searches documents (Table 3-2)."

(11) "Systematic review guidelines typically recommend at least two screeners to review each article to minimize bias. **EPA had less than 6 months to conduct data collection and screening activities for 10 chemical substances; thus, one screener was used for the title/abstract screening to meet the statutory deadline in June 2017.** However, full text screening generally used two independent screeners (see Section 3.2.2.2)."

3.3.4 Train screeners using written documentation; test and retest screeners to improve accuracy and consistency (p. 273). Rationale: Training and documentation are standard quality-assurance approaches.	EPA Systematic Review Framework is consistent with this best practice.	1						
3.3.5 Use one of two strategies to select studies: 1) read all full-text articles identified in the search or 2) screen titles and abstracts of all articles and then read the full-text of articles identified in initial screening (p. 273). Rationale: Data are not clear, even for clinical intervention questions, regarding which method is best, although 2) appears to be more common.	EPA Systematic Review Framework is unclear on this best practice.							1
3.3.6 Taking account of the risk of bias, consider using observational studies to address gaps in the evidence from randomized clinical trials on the benefits of interventions (p. 274). Rationale: Rather than exclude evidence where it is sparse, it might be necessary to use data from studies using design more susceptible to bias than a preferred design.	EPA Systematic Review Framework is consistent with this best practice. Human observational studies included in search strategy.	1						
		3	2	0	1	0		
3.4 Document the search								
3.4.1 Provide a line-by-line description of the search strategy, including the date of search for each database, web browser, etc. (p. 274) Rationale: Appropriate documentation of the search processes ensures transparency of the methods used in the review, and appropriate peer review by information specialists.	EPA Systematic Review Framework is unclear on this best practice; based on first 10 chemicals EPA Systematic Review Framework consistent with this best practice.				1	1		

3.4.2 Document the disposition of each report identified, including reasons for their exclusion if appropriate (p. 275). Rationale: The standard supports creation of a flow chart that describes the sequence of events leading to identification of included studies, and it also supports assessment of the sensitivity and precision of the searches a posteriori.

EPA Systematic Review Framework is consistent with this best practice.

1

Page 25 EPA states "Each article was generally screened by two independent reviewers using specialized web-based software (i.e., DistillerSR)¹³. Screeners were assigned batches of references after conducting pilot testing. Screening forms facilitated the reference review process by asking a series of questions based on pre-determined eligibility criteria. DistillerSR was used to manage the work flow of the screening process and document the eligibility decisions for each reference. The screeners resolved conflicts by consensus, or consultation with an independent individual(s).

Footnote 9 page 23 also states "In addition to using DistillerSR, EPA/OPPT is exploring automation and machine learning tools for data screening and prioritization activities (e.g., SWIFT-Review, SWIFT-Active Screener, Dragon, DocTER). SWIFT is an acronym for "Sciome Workbench for Interactive Computer-Facilitated Text-mining".

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3.5 Manage data collection

3.5.1 At a minimum, use two or more researchers, working independently, to extract quantitative or other critical data from each study. For other types of data, one individual could extract the data while the second individual independently checks for accuracy and completeness. Establish a fair procedure for resolving discrepancies—do not simply give final decisionmaking power to the senior reviewer (p. 275). Rationale: Because reporting is often not clear or logically placed, having two independent reviewers is a quality-assurance approach. The evidence supporting two independent data extractors is limited and so some reviewers prefer that one person extracts and the other verifies, a time- saving approach. Discrepancies would be decided by discussion so that each person’s viewpoint is heard.

EPA Systematic Review Framework is unclear on this best practice.

1

Table 3-1 states only to "Specify number and expertise of reviewers involved in the data extraction process." It does not specify that at a minimum two or more researchers working independently, will extract quantitative or other critical data from each study.

3.5.2 Link publications from the same study to avoid including data from the same study more than once (p. 276). Rationale: There are numerous examples in the literature where two articles reporting the same study are thought to represent two separate studies.

EPA Systematic Review Framework is unclear on this best practice.

1

3.5.3 Use standard data extraction forms developed for the specific systematic review (p. 276). Rationale: Standardized data forms are broadly applied quality assurance approaches.	<p>EPA Systematic Review Framework is consistent with this best practice.</p> <p>Table 3-1 states that EPA will " Extract data/information using pre-defined templates."</p> <p>page 25 EPA/OPPT will use various extraction tools to meet the needs of each chemical assessment. These may include specialized web-based software (e.g., DistillerSR, HAWC14).footnote 14 states: EPA/OPPT is exploring HAWC for extracting data supporting TSCA risk evaluations. HAWC stands for Health Assessment Workspace Collaborative.</p>	1					
3.5.4 Pilot-test the data extraction forms and process (p. 276). Rationale: Pre-testing of the data collection forms and processes are broadly applied quality assurance approaches.	<p>EPA Systematic Review Framework is consistent with this best practice.</p> <p>Table 3-1 states that EPA will "Conduct pilot study to test the extraction process and conflict resolution strategy. Unless major changes are made, piloting may only need to be conducted once and not after each update.;</p>	1					
			2	0	0	2	0
			Consistent with IOM	Inconsistent with IOM	Not Mentioned	Unclear	Not mentioned/un clear but apparently applied to First 10 TSCA chemicals
		TOTALS	12	2	6	7	5

Appendix B: Commentary in *American Journal of Public Health*

The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health



See also Morabia, p. 955; Rosner et al., p. 969; Michaels, p. 975; Samet, p. 976; Vineis, p. 978; and Rodenberg, p. 980.

Every day, the public is exposed to multiple industrial chemicals via food, water, air, and consumer products. Many are known to be toxic and can increase the risk of adverse health effects, including cancer, asthma, developmental disabilities, and infertility. The US Environmental Protection Agency (EPA) is responsible for making evidence-based policies to limit exposure to dangerous chemicals. To inform potential chemical regulations, a core component of the EPA's duty is to evaluate data on the hazards and risks of industrial chemicals under the 1976 Toxic Substances Control Act (TSCA; Pub L No. 94-469), the law covering chemicals in commerce. Congress reformed the TSCA after widespread recognition of fatal flaws in the 1976 law. Under it, the EPA could not even restrict asbestos, a known human carcinogen. In 2016, President Barack Obama signed the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Pub L No. 114-182), overhauling TSCA after 40 years. The TSCA covers more than 40 000 chemicals in the marketplace. The EPA's action (or inaction) on these

chemicals has major implications for human health in the United States because of federal law preempting states and beyond the United States because of global commerce and trade agreements.

Pursuant to implementation of the new law, the EPA's Office of Chemical Safety and Pollution Prevention recently released a methodology for collecting, evaluating, and interpreting scientific evidence on chemicals (<http://bit.ly/2TFEDrF>). The EPA officially calls the method a "systematic review" framework for TSCA, but it is systematic in name only, as it falls far short of best practices for systematic reviews. Application of the TSCA method will exclude relevant research from chemical assessments, leading to underestimation of health risks and resulting in inadequate policies that allow unsafe chemical exposures, thus harming public health. The TSCA systematic review method could be especially detrimental for populations more vulnerable to chemical exposures, such as pregnant women and children.

INTERNATIONAL CONSENSUS ON METHODS

Systematic review methodology originated more than 40 years ago in psychology and is now the standard for evaluating intervention effectiveness in evidence-based medicine. Well-conducted systematic reviews have saved lives and money by providing a comprehensive, unbiased evaluation of the evidence.¹

International scientific organizations (e.g., Cochrane and Campbell collaborations) developed, advanced, and applied the methodology. In 2009, the Navigation Guide systematic review method adapted these clinical research synthesis methods for environmental health evidence streams and decision contexts.² In 2013, the National Toxicology Program's Office of Health Assessment and Translation (OHAT) developed a comparable method (<http://bit.ly/2H9MjN7>), and scientists at

the EPA's Integrated Risk Information System program played an important role in the development and implementation of systematic review methods. Importantly, the Integrated Risk Information System's review method has been positively evaluated by the National Academies of Sciences and does not have the problems we list (<http://bit.ly/2EKyZuQ>). Peer-reviewed case studies demonstrated the value of systematic reviews in environmental health,³ and the National Academies of Sciences has recommended the Navigation Guide and OHAT's methods for chemical evaluations (<http://bit.ly/2VNzew5>).

FLAWS IN THE NEW METHODOLOGY

The 2016 TSCA law mandates that the EPA make decisions about chemical risks on the basis of the "best available science" and the "weight of the scientific evidence." The EPA defined "weight of the scientific evidence" in its 2017 regulations as follows:

a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a preestablished 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 on strengths,

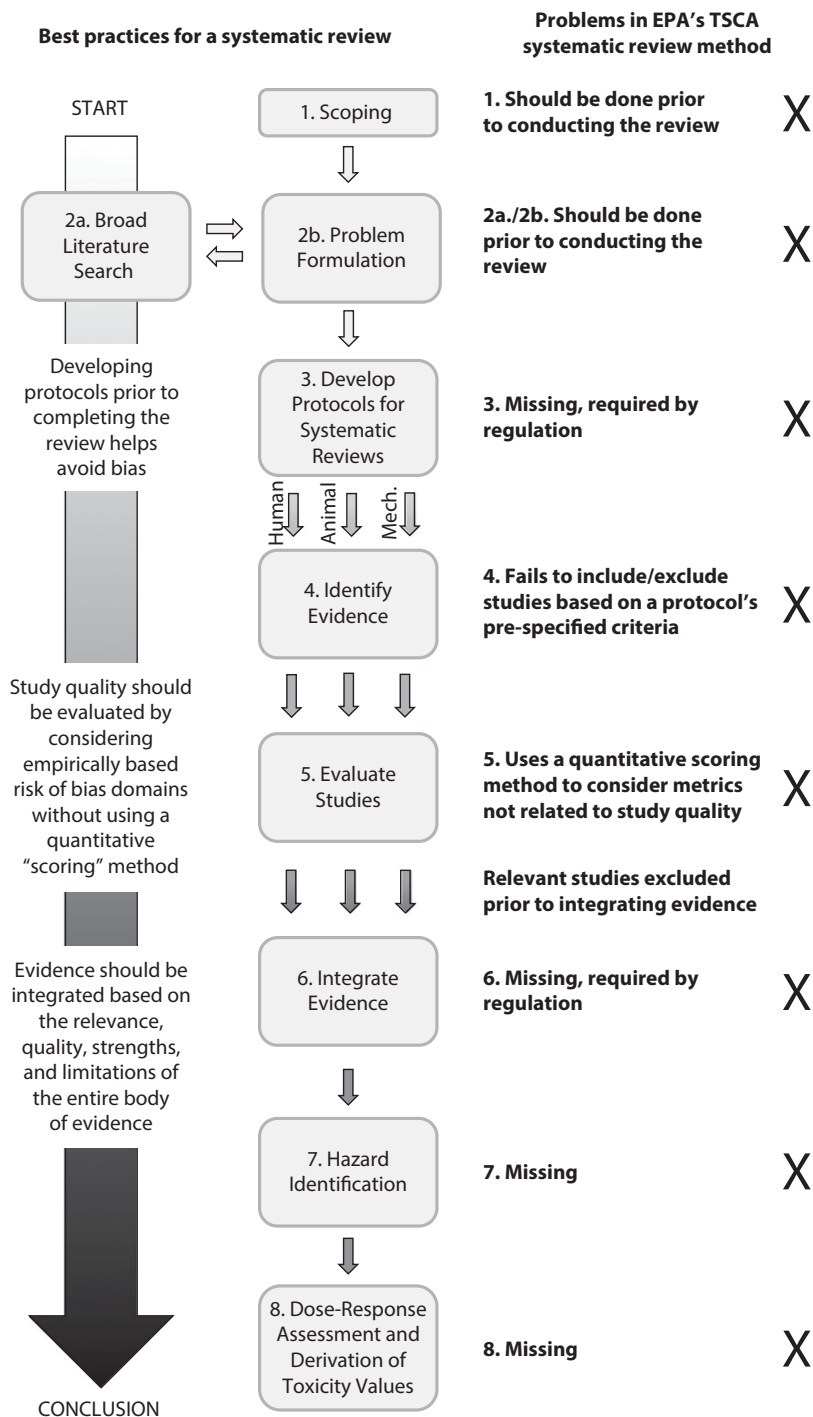
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Note. EPA = Environmental Protection Agency; Mech. = mechanistic; TSCA = Toxic Substances Control Act. The TSCA method is missing steps, does not follow established best practices for systematic review, and does not conform to regulatory requirements.

Source. Adapted from the National Academies of Sciences (<http://bit.ly/2CbAd1A>) and the Institute of Medicine (<http://bit.ly/2NRpPqk>).

FIGURE 1—A Comparison of General Steps for a Systematic Review and the Toxic Substances Control Act's Systematic Review Method

limitations, and relevance. (<http://bit.ly/2SVDGa8>)

However, instead of building on current well-established methods, the EPA issued a new TSCA methodology that is inconsistent with the definition in regulation and with empirical evidence. It also has three fundamental flaws.

INCOMPLETENESS

First, the TSCA method is incomplete. As shown in Figure 1, it lacks numerous essential systematic review elements. For example, it includes neither an explicit method for evaluating the overall body of each evidence stream (animal, human, mechanistic) nor a method for integrating two or more streams of evidence (<http://bit.ly/2NRpPqk>, <http://bit.ly/2CbAd1A>).⁴ A critical missing piece is creating protocols for all review components before conducting the review to minimize bias and ensure transparency in decision making, specified as best practice by all established methods (<http://bit.ly/2NRpPqk>, <http://bit.ly/2CbAd1A>).⁵ The EPA's 2017 regulation also requires this best practice, mandating that the agency use "a preestablished protocol" to conduct assessments.

AN INAPPROPRIATE SCORING SCHEME

Second, the TSCA systematic review method establishes an inappropriate scoring scheme for the quality of studies by assigning numerical scores to various study components and calculating an overall "quality score." The implicit assumption in quantitative scoring methods such as the EPA's is that we understand how much each factor used to evaluate study quality contributes to the

overall quality and that these factors are independent of each other. This is not a scientifically supportable underlying assumption, as researchers have documented that such scoring methods have unknown validity and may contain invalid items. Thus, results of a quality score are not predictive of the quality of studies (<http://bit.ly/2CbAd1A>).

An examination of the application of quality scores in meta-analysis found that quality score weighting produced biased effect estimates because quality is not a singular dimension that is additive, but may be nonadditive and nonlinear.⁶ The National Academies recommended against the use of scoring systems, concluding, “There is no empirical basis for weighting the different criteria in the scores. . . . The current standard in evaluation of clinical research calls for reporting each component of the assessment tool separately and not calculating an overall numeric score” (<http://bit.ly/2CbAd1A>). In addition, the new TSCA methodology scores study components that are unrelated to research quality, for instance, how completely the authors of a study reported the methods used. This will result in a biased evaluation of the literature.

INCENTIVES TO DISREGARD RELEVANT RESEARCH

Third, the new TSCA methodology could disregard relevant research findings because it uses this scoring scheme to exclude studies that have only a single reporting or methodological limitation. It is inappropriate to use a single limitation to exclude relevant studies, as the EPA’s 2017 regulation requires consideration of all relevant

science while accounting for “strengths and limitations.” This is also consistent with approaches in established systematic review methodologies (<http://bit.ly/2VNz5w5>, <http://bit.ly/2H9MjN7>).⁴ Furthermore, there is no empirical evidence that the “critical metrics” the EPA uses to exclude studies are related to study quality. For example, to score human epidemiology studies, some critical metrics are whether the eligibility criteria, sources, and methods for selecting participants were reported. If not reported, the study may be scored “low quality” or “unacceptable for use.” It has, however, been documented that how completely and clearly a study is reported is not a valid measure of the quality of the underlying research.⁷ Thus the TSCA criteria could exclude many high-quality epidemiological studies. The first application of the TSCA method in evaluations of five persistent, bioaccumulative, and toxic chemicals excluded almost 500 studies that “did not meet evaluation criteria” of the new methodology (<http://bit.ly/2XPVWp0>).

In summary, the TSCA method ignores significant scientific and internationally accepted rules and procedures for conducting systematic reviews, which will result in incomplete and biased chemical evaluations—ultimately leading to policy decisions on billions of pounds of industrial chemicals that threaten public health. We recommend that for TSCA evaluations, the EPA adopt and implement existing empirically based methodology as the National Academies recommends for chemical evaluations (<http://bit.ly/2VNz5w5>, <http://bit.ly/2H9MjN7>, <http://bit.ly/2EKyZuQ>).³ Using these methods would enable the EPA to make the best science-based

decisions to protect the environment and human health. **AJPH**

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CONTRIBUTORS

V. I. Singla drafted the editorial. P. M. Sutton conducted the analysis. P. M. Sutton and T. J. Woodruff conducted revisions and review.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Appendix C.1: Chlorinated Phosphate Ester (CPE) Cluster; TSCA Section 21 Petition

not interfere with continued maintenance of the 1997 ozone NAAQS in the Area Middle Tennessee Area, or with any other applicable CAA requirement, has been placed in the public docket for this action.

V. Legal Authority

The statutory authority for this action is granted to the EPA by Sections 211(h) and 301(a) of the Clean Air Act, as amended; 42 U.S.C. 7545(h) and 7601(a).

List of Subjects in 40 CFR Part 80

Environmental protection, Administrative practice and procedures, Air pollution control, Fuel additives, Gasoline, Incorporation by reference, Motor vehicle and motor vehicle engines, Motor vehicle pollution, Penalties, Reporting and recordkeeping requirements.

Dated: April 4, 2017.

E. Scott Pruitt,
Administrator.

[FR Doc. 2017-07399 Filed 4-11-17; 8:45 am]

BILLING CODE 6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Chapter I

[EPA-HQ-OPPT-2017-0038; FRL-9961-04]

Chlorinated Phosphate Ester (CPE) Cluster; TSCA Section 21 Petition; Reasons for Agency Response

AGENCY: Environmental Protection Agency (EPA).

ACTION: Petition; reasons for Agency response.

SUMMARY: This document provides the reasons for EPA's response to a petition it received under the Toxic Substances Control Act (TSCA). The TSCA section 21 petition was received from Earthjustice, Natural Resources Defense Council, Toxic-Free Future, Safer Chemicals, Healthy Families, BlueGreen Alliance, and Environmental Health Strategy Center on January 6, 2017. The petitioners requested that EPA issue an order under TSCA section 4, requiring that testing be conducted by manufacturers and processors of chlorinated phosphate esters ("CPE"). The CPE Cluster is composed of tris(2-chloroethyl) phosphate ("TCEP") (CAS No. 115-96-8), 2-propanol, 1-chloro-, phosphate ("TCPP") (CAS No. 13674-84-5), and 2-propanol, 1,3- dichloro-, phosphate ("TDCPP") (CAS No. 13674-87-8). After careful consideration, EPA denied the TSCA section 21 petition for the reasons discussed in this document.

DATES: EPA's response to this TSCA section 21 petition was signed April 6, 2017.

FOR FURTHER INFORMATION CONTACT:

For technical information contact: Hannah Braun, Chemical Control Division (7405M), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460-0001; telephone number: (202) 564-5614; email address: braun.hannah@epa.gov.

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1404; email address: TSCA-Hotline@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

This action is directed to the public in general. This action may, however, be of interest to those persons who are or may manufacture or process the chemicals tris(2-chloroethyl) phosphate ("TCEP") (CAS No. 115-96-8), 2-propanol, 1-chloro-, phosphate ("TCPP") (CAS No. 13674-84-5), and 2-propanol, 1,3- dichloro-, phosphate ("TDCPP") (CAS No. 13674-87-8). Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. How can I access information about this petition?

The docket for this TSCA section 21 petition, identified by docket identification (ID) number EPA-HQ-OPPT-2017-0038, is available at <http://www.regulations.gov> or at the Office of Pollution Prevention and Toxics Docket (OPPT Docket), Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave. NW., Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPPT Docket is (202) 566-0280. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

II. TSCA Section 21

A. What is a TSCA section 21 petition?

Under TSCA section 21 (15 U.S.C. 2620), any person can petition EPA to initiate a rulemaking proceeding for the

issuance, amendment, or repeal of a rule under TSCA section 4, 6, or 8 or an order under TSCA section 4 or 5(e) or (f). A TSCA section 21 petition must set forth the facts that are claimed to establish the necessity for the action requested. EPA is required to grant or deny the petition within 90 days of its filing. If EPA grants the petition, the Agency must promptly commence an appropriate proceeding. If EPA denies the petition, the Agency must publish its reasons for the denial in the **Federal Register**. A petitioner may commence a civil action in a U.S. district court to compel initiation of the requested rulemaking proceeding within 60 days of either a denial or the expiration of the 90-day period.

B. What criteria apply to a decision on a TSCA section 21 petition?

1. *Legal standard regarding TSCA section 21 petitions.* Section 21(b)(1) of TSCA requires that the petition "set forth the facts which it is claimed establish that it is necessary" to issue the rule or order requested. 15 U.S.C. 2620(b)(1). Thus, TSCA section 21 implicitly incorporates the statutory standards that apply to the requested actions. Accordingly, EPA has relied on the standards in TSCA section 21 and in the provisions under which actions have been requested to evaluate this TSCA section 21 petition. In addition, TSCA section 21 establishes standards a court must use to decide whether to order EPA to initiate an order in the event of a lawsuit filed by the petitioner after denial of a TSCA section 21 petition. 15 U.S.C. 2620(b)(4)(B).

2. *Legal standard regarding TSCA section 4 rules.* EPA must make several findings in order to issue a rule or order to require testing under TSCA section 4(a)(1)(A)(i). In all cases, EPA must find that information and experience are insufficient to reasonably determine or predict the effects of a chemical substance on health or the environment and that testing of the chemical substance is necessary to develop the missing information. 15 U.S.C. 2603(a)(1). In addition, EPA must find that the chemical substance may present an unreasonable risk of injury under section 4(a)(1)(A)(i). *Id.* If EPA denies a petition for a TSCA section 4 rule or order and the petitioners challenge that decision, TSCA section 21 allows a court to order EPA to initiate the action requested by the petitioner if the petitioner demonstrates to the satisfaction of the court by a preponderance of the evidence in a *de novo* proceeding that findings very similar to those described in this unit

with respect to a chemical substance have been met.

III. Summary of the TSCA Section 21 Petition

A. What action was requested?

On January 6, 2017, Earthjustice, Natural Resources Defense Council, Toxic-Free Future, Safer Chemicals, Healthy Families, BlueGreen Alliance, and Environmental Health Strategy Center petitioned EPA to issue an order under TSCA section 4(a)(1), 90 days after the petition was filed, requiring that testing be conducted by manufacturers and processors of the chlorinated phosphate esters (“CPE”) Cluster composed of tris(2-chloroethyl) phosphate (“TCEP”) (CAS No. 115–96–8), 2-propanol, 1-chloro-, phosphate (“TCPP”) (CAS No. 13674–84–5), and 2-propanol, 1,3- dichloro-, phosphate (“TDCPP”) (CAS No. 13674–87–8) (Ref. 1).

B. What support do the petitioners offer?

The petitioners cite to section 4(a)(1) of TSCA, which requires EPA to direct testing on a chemical substance or mixture if the Administrator finds the following criteria are met:

1. The manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment.
2. There is insufficient information and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture, or of any combination of such activities on health or the environment can reasonably be determined or predicted.
3. Testing is necessary to develop such information.

The petitioners assert that the CPE Cluster chemicals “may present an unreasonable risk of injury to health or the environment” because there is substantial evidence that chemicals in the CPE Cluster may be toxic, including:

- EPA’s TSCA Work Plan Chemical Problem Formulation and Initial Assessment—Chlorinated Phosphate Ester Cluster Flame Retardants (heretofore referred to as Problem Formulation and Initial Assessment), which cites multiple mammalian toxicity studies showing adverse effects caused by the cluster members such as reproductive and developmental effects, neurological effects, liver, kidney and thyroid effects and cancer (for certain cluster members) (Refs. 2–7).
- EPA’s Problem Formulation and Initial Assessment, which also states

that ecological toxicity from exposure to TCEP and TDCPP was exhibited in acute tests with fish resulting in loss of coordination, edema, darker pigmentation and hyperventilation (Ref. 2).

- EPA’s Design for the Environment in which the Agency conducted a hazard assessment of the chemicals in the CPE cluster and found that each of the three cluster members are considered a high hazard for more than one human health effect, as well as for aquatic toxicity, based on empirical data. Additionally, TCPP and TDCPP are considered to be highly persistent (Ref. 8).

- The state of California finds TDCPP to be a “known carcinogen,” and in 2011 California added TDCPP to the list of chemicals requiring warning labels under California Proposition 65 law (Ref. 9, 10).

- California’s Proposition 65 list of chemicals where TCEP was “known to the State to cause cancer” in 1992 (Ref. 11).

- The European Union (EU) classifying TCEP as a “Substance of Very High Concern” based on reproductive toxicity (Ref. 12).

- California’s Safer Consumer Products program listing TCPP as a candidate chemical based on carcinogenicity (Ref. 13).

The petitioners assert there are CPE Cluster chemicals exposure to humans and the environment based on the following information provided in EPA’s Problem Formulation and Initial Assessment (Ref. 2).

- Several studies of U.S. drinking water where CPEs have been detected (Refs. 14–16).
- Numerous studies where concentrations of CPEs in infant products such as high chairs, bath mats, car seats, nursing pillows, carriers, sofas, and camping tents have been measured (Refs. 17–21).

- Small children may have additional exposures through contact with baby products containing CPEs and via mouthing behaviors (Ref. 2).

- A number of published studies where levels of CPEs in indoor air and dust have been reported (Refs. 19–49).

- Several studies throughout the United States and abroad which reported levels of the CPEs in surface water. Collectively, these data indicate high potential for exposures to ecological receptors, and in particular, aquatic organisms (Refs. 50–77).

- A study where TCEP, TCPP, and TDCPP have all been measured in herring gull eggs from the Lake Huron area (Ref. 78).

With the evidence of toxicity and exposure the petitioners argue that the chemicals in the CPE Cluster meet the criteria for “may present an unreasonable risk of injury to health or the environment.”

The petitioners also assert there is “insufficient information” on the CPE Cluster chemicals. They indicate that EPA’s Problem Formulation and Initial Assessment (Ref. 2) “identifies seven critical data gaps around exposures and hazards of these flame retardants”. While EPA disagrees that the Problem Formulation and Initial Assessment specifically identifies those which the petitioners assert, the petition lists the following seven data gaps around exposures and hazard of CPE flame retardants:

- Exposure pathways: Dermal and inhalation;
- 2. Hazard: Reproduction and endocrine toxicity;
- 3. Exposure: Environmental releases from non-industrial uses;
- 4. Exposure: Community and worker exposures from manufacturing, processing, industrial and non-industrial uses;
- 5. Exposure: Community and worker exposures recycling;
- 6. Exposure: Community, worker and environmental exposures from disposal; and
- 7. Hazard: Toxicity to birds, wildlife, sediment organisms.

The petitioners argue that the testing recommended in the petition is critical to address this allegedly insufficient information and for performing any TSCA section 6 risk evaluation of the CPE Cluster chemicals.

IV. Disposition of TSCA Section 21 Petition

A. What was EPA’s response?

After careful consideration, EPA denied the petition. A copy of the Agency’s response, which consists of two letters to the signatory petitioners from Earthjustice and Natural Resources Defense Council (Ref. 79), is available in the docket for this TSCA section 21 petition.

B. Background Considerations for the Petition

EPA published a Problem Formulation and Initial Assessment for the CPE Cluster chemicals in August 2015 (Ref. 2). As stated on EPA’s Web site titled “Assessments for TSCA Work Plan Chemicals” (Ref. 80), “As a first step in evaluating TSCA Work Plan Chemicals, EPA performs problem formulation to determine if available data and current assessment approaches

and tools will support the assessments.” During development of the Problem Formulation and Initial Assessment document for the CPE Cluster chemicals, EPA followed an approach developed for assessing chemicals under TSCA as it existed at that time. In addition, in Table 2–1 of the Problem Formulation and Initial Assessment (Ref. 2), EPA specified, in very general terms, the nature and type of information sought to inform this particular risk assessment, under the existing TSCA framework.

Under TSCA prior to the June amendments, EPA performed risk assessments on individual uses, hazards, and exposure pathways. The approach taken during the TSCA Work Plan assessment effort was to focus risk assessments on those conditions of use that were most likely to pose concern, and for which EPA identified the most robust readily available, existing, empirical data, located using targeted literature searches, although modeling approaches and alternative types of data were also considered. EPA relied heavily on previously conducted assessments by other authoritative bodies and well-established conventional risk assessment methodologies in developing the Problem Formulation documents. Although EPA identified existing information and presented it in the Problem Formulation and Initial Assessment, EPA did not necessarily undertake a comprehensive search of available information or articulate a range of scientifically supportable approaches that might be used to perform risk assessment for various uses, hazards, and exposure pathways in the absence of directly applicable, empirical data prior to seeking public input. Rather, EPA generally elected to focus its attention on the uses, hazards, and exposure pathways that appeared to be of greatest concern and for which the most extensive relevant information had been identified. (Ref. 2).

As EPA explains on its Web site, “Based on on-going experience in conducting TSCA Work Plan Chemical assessments and stakeholder feedback, starting in 2015 EPA will publish a problem formulation for each TSCA Work Plan assessment as a stand-alone document to facilitate public and stakeholder comment and input prior to conducting further risk analysis. Commensurate with release of a problem formulation document, EPA will open a public docket for receiving comments, data or information from interested stakeholders. EPA believes publishing problem formulations for TSCA Work Plan assessments will

increase transparency of EPA’s thinking and analysis process, provide opportunity for public/stakeholders to comment on EPA’s approach and provide additional information/data to supplement or refine our assessment approach prior to EPA conducting detailed risk analysis and risk characterization” (Ref. 80).

EPA’s 2015 Problem Formulation and Initial Assessment for the CPE Cluster chemicals does not constitute a full risk assessment for the chemicals in the CPE Cluster, nor does it purport to be a final analysis plan for performing a risk assessment or to present the results of a comprehensive search for available data or approaches for conducting risk assessments. Rather, it is a preliminary step in the risk assessment process, which EPA desired to publish to provide transparency and the opportunity for public input. EPA received comments from Earthjustice, Natural Resources Defense Council and others during the public comment period, which ended in November 2015 (Ref. 81). After the public comment period, EPA was in the process of considering this input in refining the analysis plan and further data collection for conducting a risk assessment for the CPE Cluster chemicals.

On June 22, 2016, Congress passed the Frank R. Lautenberg Chemical Safety for the 21st Century Act. EPA has interpreted the amended TSCA as requiring that forthcoming risk evaluations encompass all manufacturing, processing, distribution in commerce, use, and disposal activities that the Administrator determines are intended, known, or reasonably foreseen (Ref. 83). This interpretation of “conditions of use” as defined by TSCA section 3(4), has prompted EPA to re-visit the scoping and problem formulation for risk assessments under TSCA. Other provisions included in the amended TSCA, including section 4(h) regarding alternative testing methods, have also prompted EPA to evolve its approach to scoping and conducting risk evaluations. The requirement to consider all conditions of use in risk evaluations—and to do so during the three to three and a half years allotted in the statute—has led EPA to more fully evaluate the range of data sources and technically sound approaches for conducting risk evaluations. Thus, a policy decision articulated in a problem formulation under the pre-amendment TSCA not to proceed with risk assessment for a particular use, hazard, or exposure pathway does not necessarily indicate at this time that EPA will need to require testing in order

to proceed to risk evaluation. Rather, such a decision indicates an area in which EPA will need to further evaluate the range of potential approaches—including generation of additional test data—for proceeding to risk evaluation. EPA is actively developing and evolving approaches for implementing the new provisions in amended TSCA. These approaches are expected to address many, if not all, of the data needs asserted in the petition. Whereas under the Work Plan assessment effort, EPA sometimes opted not to include conditions of use for which data were limited or lacking, under section 6 of amended TSCA, EPA will evaluate all conditions of use and will apply a broad range of scientifically defensible approaches—using data, predictive models, or other methods—that are appropriate and consistent with the provisions of TSCA section 26, to characterize risk and enable the Administrator to make a determination of whether the chemical substance presents an unreasonable risk.

C. What was EPA’s reason for this response?

For the purpose of making its decision on the response to the petition, EPA evaluated the information presented or referenced in the petition and its authority and requirements under TSCA sections 4 and 21. EPA also evaluated relevant information that was available to EPA during the 90-day petition review period that may have not been available or identified during the development of EPA’s Problem Formulation and Initial Assessment (Ref. 2).

EPA agrees that the manufacture, distribution in commerce, processing, use, or disposal of the CPE Cluster chemicals may present an unreasonable risk of injury to health or the environment under TSCA section 4(a)(1)(A). EPA also agrees that the Problem Formulation and Initial Assessment was not comprehensive in scope with regard to the conditions of use of the CPE Cluster chemicals, exposure pathways/routes, or potentially exposed populations. However, the Problem Formulation and Initial Assessment was not designed to be comprehensive. Rather, the Problem Formulation and Initial Assessment was developed under EPA’s then-existing process, as explained previously. It was a fit-for-purpose document to meet a TSCA Work Plan (*i.e.*, pre-Lautenberg Act) need. Going forward under TSCA, as amended, EPA will conform its analyses to TSCA, as amended. EPA has explained elsewhere how the Agency proposes to conduct prioritization and

risk evaluation going forward (Refs. 82 and 83). However, EPA does not find that the petitioners have demonstrated, for each exposure pathway and hazard endpoint presented in the petition, that the information and experience available to EPA are insufficient to reasonably determine or predict the effects on health or the environment from “manufacture, distribution in commerce, processing, use, or disposal” (or any combination of such activities) of the CPE Cluster chemicals nor that the specific testing they have identified is necessary to develop such information.

The discussion that follows provides the reasons for EPA’s decision to deny the petition based on the finding that for each requested test the information on the individual exposure pathways and hazard endpoints identified by the petitioners do not demonstrate that there is insufficient information upon which the effects of the CPE Cluster chemicals can reasonably be determined or predicted or that the requested testing is necessary to develop additional information. The sequence of EPA’s responses follows the sequence in which requested testing was presented in the petition (Ref. 1). 1. *Dermal and Inhalation Exposure Toxicity. a. Dermal toxicity.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects to health from dermal exposure to the CPE Cluster chemicals. The toxicokinetics test (Organization for Economic Co-operation and Development (OECD) Test Guideline 417) (Ref. 84), in vivo absorption test (OECD Test Guideline 427) (Ref. 85) and dermal toxicity test (OPPTS Test Guideline 870.1200) (Ref. 86) requested by the petitioners may not be needed. In the Problem Formulation and Initial Assessment, EPA stated that risk from the dermal exposure pathway could not be quantified for risk assessment because of a lack of route-specific toxicological data, but also indicated that an alternative approach, *i.e.*, development of a PBPK model for oral, inhalation and dermal routes of exposure would provide the ability to perform route-to-route extrapolation. The Problem Formulation and Initial Assessment indicated that adequate toxicokinetic data would be needed for each route of exposure and that these data are lacking for dermal exposures. However, since the publication of the Problem Formulation and Initial Assessment document, EPA has identified pharmacokinetic data including absorption, bioaccessibility

and absorption, distribution, metabolism and excretion (ADME) data (Refs. 7, 87–96) that could be used to perform route-to-route extrapolation from oral toxicity studies to predict effects from dermal exposure to the CPE Cluster chemicals.

Furthermore, EPA’s use of available existing toxicity information reduces the use of vertebrate animals in the testing of chemical substances in a manner consistent with provisions described in TSCA section 4(h).

b. *Inhalation toxicity.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects to health from inhalation exposure to the CPE Cluster chemicals. The toxicokinetics test (OECD Test Guideline 417: Toxicokinetics) (Ref. 84) and inhalation toxicity test (OPPTS Test Guideline 870.1300: Acute Inhalation Toxicity) (Ref. 98) requested by the petitioners may not be needed. In the Problem Formulation and Initial Assessment, EPA stated that risk from the inhalation exposure pathway could not be quantified for risk assessment because of a lack of route-specific toxicological data, but also indicated that an alternative approach, *i.e.*, development of a PBPK model for oral, inhalation and dermal routes of exposure would provide the ability to perform route-to-route extrapolation. The Problem Formulation and Initial Assessment, indicated that adequate toxicokinetic data would be needed for each route of exposure and that these data are lacking for inhalation exposures. However, since the publication of the Problem Formulation and Initial Assessment, EPA has identified toxicological data including, acute toxicity, bioaccessibility and ADME data (Refs. 7, 87–89, 93, 99 and 100) that could be used in route-to-route extrapolation from oral toxicity studies to predict effects from inhalation exposure to the CPE Cluster chemicals. As proposed in the Problem Formulation and Initial Assessment, CPE Cluster chemicals that are absorbed to and inhaled associated with particles, once the particles are in the gastrointestinal tract, absorption would be the same as in the oral toxicity studies and hence, oral toxicity studies can be used to determine or predict effects to health from inhalation exposure to the CPE cluster substances. Current literature on bioaccessibility (Ref. 89) could also be used to refine the estimate of the amount of the CPE Cluster chemicals absorbed via ingestion of particles (via inhalation and translocation to the gut).

Furthermore, EPA’s use of available existing toxicity information reduces the use of vertebrate animals in the testing of chemical substances in a manner consistent with provisions described in TSCA section 4(h). 2. *Reproductive and Endocrine Toxicity. a. Reproductive Toxicity.* The petition does not set forth facts demonstrating that there is insufficient data available to EPA to reasonably determine or predict the reproductive toxicity of the CPE Cluster chemicals. The NTP Modified One Generation study (Ref. 102) or the alternatively suggested in vivo reproductive toxicity screening test (OPPTS 870.3800: Reproduction and Fertility Effects) (Ref. 103) based on two-generation reproduction toxicity test (OECD Test Guideline 416) (Ref. 104), requested by the petitioners, may not be needed. Although EPA states in the Problem Formulation and Initial Assessment that “given uncertainty surrounding the impact of long-term exposures and male reproductive toxicity, it would not be possible to quantify risks at this time,” EPA now believes, after further review and consideration of existing studies, that the Agency could use information identified in the Problem Formulation and Initial Assessment, as well as new information identified through comprehensive literature searches, data from alternative testing approaches, and read-across (in which data for one structurally similar chemical can be used to assess the toxicity of another) could be used to conduct an assessment of effects of the CPE Cluster chemicals on reproduction (Ref. 2). As presented in the Problem Formulation and Initial Assessment, EPA identified several studies for each chemical in the CPE Cluster to assess reproductive effects. Specifically, a multi-generation reproductive and developmental toxicity study in mice for TCEP (Ref. 105) and a two-generation reproductive and developmental study in rats for TCPP (Ref. 106, test data currently listed as CBI) were identified. For TDCPP, a reproduction study in male rabbits (Ref. 7), two developmental toxicity studies in female rats (Refs. 7 and 107) and a two-year cancer bioassay in rats, which included evaluation of effects on reproductive organs (Ref. 108), are already available.

Since the publication of the Problem Formulation Initial Assessment document, EPA identified additional reproductive studies. Specifically, TCPP has been evaluated in a developmental toxicity study (Ref. 109). The results of this study have not yet been released, but are expected to be available to EPA

prior to initiation of a Risk Evaluation for TCPP. EPA has also identified studies using alternative animal models and *in vitro* tests that could inform the evaluation of reproductive toxicity (Refs. 110–117). Finally, given the structural similarity of the three chemicals in the CPE Cluster, EPA could consider read-across approaches, using data from one chemical to characterize the hazards of another chemical. Collectively, the studies identified in the Problem Formulation and Initial Assessment document, the studies identified since the release of the Problem Formulation and Initial Assessment document, and read-across approaches, could be used to characterize reproductive toxicity for the CPE Cluster chemicals.

Furthermore, EPA's use of available existing toxicity information reduces the use of vertebrate animals in the testing of chemical substances in a manner consistent with provisions described in TSCA section 4(h).

b. Endocrine Activity. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict the effects of the CPE Cluster chemicals on endocrine activity. EPA believes that the Larval Amphibian Growth and Development Assay (OCSPP 890.2300) (Ref. 118) or the alternatively suggested NTP Modified One Generation Study (Ref. 102) requested by the petitioners may not be needed. EPA's Problem Formulation and Initial Assessment stated that data were conflicting with regard to endocrine activity, which made it difficult to make a determination in the pre-assessment phase. However, EPA did not consider the information to be insufficient; rather EPA intended to defer drawing conclusions until the assessment phase when additional, comprehensive review of all available data would be conducted.

A number of studies evaluating thyroidal and other endocrine effects are available, including the reproduction and developmental toxicity studies described in Unit IV.C.2.a. (Refs. 7, 105, 106 and 108), as well as studies using alternative animal models and *in vitro* tests (Refs. 110–117) identified since the Problem Formulation and Initial Assessment. An evaluation of each study as well as the full body of

evidence (*i.e.*, weight of evidence) would be undertaken to identify endocrine-related hazard concerns. 3. *Environmental Releases from Non-Industrial and Consumer Uses.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects of the CPE Cluster chemicals associated with environmental releases from non-industrial and consumer uses nor specifically the potential contribution of down-the-drain releases of the CPE Cluster chemicals in United States waters. EPA agrees with the petitioner's suggestion that existing data (*e.g.*, effluent and influent of wastewater) could be used to estimate environmental concentrations of the CPE Cluster chemicals from consumer and down-the-drain uses. Hence, development of sampling plans for effluent waters from municipal treatment plants and analytical methods for measuring the CPE Cluster chemicals may not be needed.

While EPA's Problem Formulation and Initial Assessment indicated that contributions of non-industrial and consumer uses to water and wastewater were not quantifiable, EPA's conceptual model did indicate that exposures to water and wastewater (aggregated from all sources) would be assessed. EPA agrees, as the petition suggests, that existing effluent and influent from wastewater could likely be used to predict environmental concentrations of the CPE Cluster chemicals from consumer and other down-the-drain uses. As identified in the Problem Formulation and Initial Assessment, there are over 100 available monitoring studies that could be used to characterize concentrations of the CPE Cluster chemicals in water and wastewater. Monitoring studies range from nationwide studies with larger sample sizes and consistent analytical methods such as United States Geological Survey (USGS), to targeted studies with generally smaller sample sizes and variable analytical methods.

In addition, several studies from other countries are also available to characterize the CPE Cluster chemicals in water and wastewater. Since the publication and Problem Formulation and Initial Assessment document, an Australian study (Ref. 124), sampled for all three members of the CPE Cluster in

11 waste water treatment plants (Ref. 124). Another study, identified in the Problem Formulation and Initial Assessment, compares influent water concentrations between the U.S. and Sweden (Ref. 29) and indicates that U.S. concentration values are comparable to Sweden, suggesting that data from Sweden could also be considered in a U.S. assessment.

EPA has identified existing effluent data from municipal treatment plants for TCEP and TDCPP from the U.S. Geological Survey National Water Information System (Ref. 121) since the publication of the Problem Formulation and Initial Assessment document. Several other studies also indicate the presence of CPE Cluster chemicals in U.S. wastewater (Refs. 55 and 122). One study shows low levels of TCEP in a sample from U.S. industrial laundry wastewater (Ref. 123), a potential down-the-drain contributor to treatment plant effluent. Other wastewater samples in the industrial laundry study showed non-detect levels of TCEP. EPA agrees with the petitioners that these types of data may be especially useful to estimate potential contributions from down-the-drain uses to water and wastewater CPE concentrations. Hence, as the petitioners suggest, EPA could use a combination of existing occurrence data, especially effluent and influent of wastewater from municipal treatment plants (*e.g.*, U.S. effluent data and non-U.S. data) to determine or predict contributions from non-industrial and consumer uses, including the potential contribution of down-the-drain releases. EPA believes that the monitoring and effluent data described previously, as well as additional data that describes non-industrial or consumer sources to wastewater (Ref. 125) that may be identified during prioritization of the CPE Cluster for risk evaluation is likely sufficient for characterizing risk from exposures to water and wastewater and for assessing potential contributions from non-industrial and consumer down-the-drain releases of the CPE Cluster chemicals. As the petitioners point out, this approach of using existing monitoring data and especially wastewater effluent data has been used by others (*i.e.*, Environment and Climate Change Canada) to assess the potential contribution to down-the-drain releases (Ref. 2).

EPA believes that the development of analytical methods for the determination and quantification of the CPE Cluster chemicals in sampled waters and the development of a strategy for sampling effluent waters from municipal treatment plants as requested by the petitioners is not needed at this time. Analytical methods for TCEP, TCPP and TDCPP already exist as evidenced by measurements performed by the USGS and other laboratories (Refs. 119 and 120). The petition does not establish why these are insufficient. *4. Exposure from manufacturing, processing, industrial and non-industrial uses. a.*

Communities. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure to air, soil and water in communities near manufacturing, processing, industrial and non-industrial use facilities of the CPE Cluster chemicals. The petitioners state that in the absence of facility specific Toxic Release Inventory (TRI) data, other information sources should be used to identify relevant facilities to monitor near. EPA agrees with the petitioners that other sources of information, such as Chemical Data Reporting (CDR), can be used to identify relevant facilities on which exposure estimates could be made.

Although the Problem Formulation and Initial Assessment states that chemical-specific environmental release data to air, soil and water from industrial sites could not be found (Ref. 2), EPA believes that approaches other than site-specific monitoring could be used to assess potential exposures from manufacturing, processing, industrial and non-industrial uses. EPA believes it could be reasonable to estimate or model releases from facilities and concentrations in the surrounding environments using established EPA models such as ChemSTEER, E-FAST and AERMOD. ChemSTEER is a model to estimate workplace exposure and environmental releases (Ref. 126). E-FAST is a tool to estimate concentrations of chemicals released to air, water, landfills and consumer products (Ref. 127). AERMOD is a model to estimate chemical emissions from stationary industrial sources (Ref. 128). All of these models have been extensively reviewed and validated based on comparisons with monitoring data. These modeled estimates could be compared to existing U.S. monitoring data, which is not site-specific, and non-U.S. data associated with industrial facilities to assess the modeling

approaches. Monitoring data exist for the CPE Cluster chemicals. As identified in the Problem Formulation Initial Assessment, there are over 100 available monitoring studies that could be used to characterize concentrations of the CPE Cluster chemicals in various media (Ref. 2).

Air. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure through air in communities near manufacturing, processing, industrial and non-industrial use facilities of the CPE Cluster chemicals. Air sampling, using methods such as EPA Air Method Toxic Organics-9A (TO-9A, Determination of Polychlorinated, Polybrominated and Brominated/Chlorinated Dibenzo-p-Dioxins and Dibenzofurans in Ambient Air) (Ref. 129), in the vicinity of representative manufacturing and processing facilities, as requested by the petitioners may not be necessary. EPA could use existing approaches, such as modeling (ChemSTEER, E-FAST and AERMOD) (Refs. 126–128) along with existing data to estimate releases and air concentrations near facilities for the CPE Cluster chemicals.

The modeled data in combination with measurements of the CPE Cluster chemicals in ambient air as identified in the Problem Formulation and Initial Assessment for the U.S. and abroad (Refs. 40, 49, 130 and 131), could be used to estimate air concentrations in communities near manufacturing and processing facilities. However, the petition does not address these possibilities, let alone explain why a testing order under section 4 would be necessary at this point. EPA considers this approach to be reasonable to determine exposure to communities near manufacturing and processing facilities, but may decide to pursue targeted sampling in the future near manufacturing and processing facilities to reduce uncertainty.

Soil. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure through soil in communities near manufacturing, processing, industrial and non-industrial use facilities of the CPE Cluster chemicals. Soil sampling, using EPA methods, in the vicinity of representative manufacturing and processing facilities, as requested by the petitioners may not be necessary. Although the Problem Formulation and Initial Assessment stated that “Studies of soil with measured U.S. values are not readily available” (Ref. 2 Page 67),

EPA could use a combination of models (e.g. ChemSTEER and AERMOD) to predict deposition to soil near facilities in conjunction with predicted environmental releases to air. The modeled data in combination with measurements of the CPE Cluster chemicals in other media such as sludge, biosolids, and effluent as identified in the Problem Formulation and Initial Assessment (Refs. 40, 55, 122, 132 and 133) could be used to estimate soil concentrations from land application of sludge and effluent. There is also a study in Germany, identified since the publication of the Problem Formulation and Initial Assessment, showing concentrations (ranging from approximately 2–20 µg/kg dry weight) of TCEP and TCPP in soil from grasslands and two urban sites (Ref. 134) which also could be evaluated for use in predicting soil concentrations in communities near manufacturing and processing facilities. However, the petition does not address these possibilities, let alone explain why a testing order under section 4 would be necessary at this point. EPA considers this approach to be reasonable to determine exposure to communities near manufacturing and processing facilities, but may decide to pursue targeted sampling in the future near manufacturing and processing facilities to reduce uncertainty.

Water. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure through water in communities near manufacturing, processing, and industrial and non-industrial use facilities of the CPE Cluster chemicals. Sampling studies, especially for various types of water (e.g., drinking water, surface water, and ground water) may not be necessary. EPA could use existing measured chemical-specific environmental data and modeling to estimate releases and water concentrations near facilities.

For example, surface water concentrations near known facilities can be estimated using existing approaches, such as E-FAST and ChemSTEER along with estimated releases from these activities (Refs. 126 and 127). As identified in the Problem Formulation and Initial Assessment, data are available for surface water concentrations of TCEP and TDCPP from USGS NWIS as well as other studies. Surface water monitoring data for TCPP are available in the open literature (Refs. 50, 55 and 135). Groundwater concentrations near known facilities can also be characterized using models such as E-

FAST and ChemSTEER (Refs. 126 and 127).

Furthermore, groundwater data are available for TCEP and TDCPP from USGS NWIS in addition to other monitoring studies that have reported concentrations (generally ranging from non-detect to approximately 1 µg/L) for all three CPE Cluster chemicals (Refs. 65 and 136).

As with surface and groundwater, drinking water concentrations near known facilities could also be estimated from releases using modeling (e.g., E-FAST and ChemSTEER). Furthermore, drinking water data from samples taken at drinking water treatment plants are available for TCEP, TCEP and TDCPP from several studies that have reported concentrations generally ranging from non-detect to approximately 1 µg/L (Refs. 14–16 and 137).

In summary, EPA could use modeled data in combination with measurements of the CPE Cluster chemicals in water to estimate water concentrations in communities near manufacturing and processing facilities. However, the petition does not address these possibilities, let alone explain why a testing order under section 4 would be necessary at this point. EPA considers this approach to be reasonable to determine exposure to communities near manufacturing and processing facilities, but may decide to pursue targeted sampling in the future near manufacturing and processing facilities to reduce uncertainty.

b and c. Workers (Industrial and Non-Industrial). The petition states that “Occupational assessments, including biological and environmental monitoring, should be conducted in representative manufacturing, processing and industrial use facilities” and that “Occupational assessments based on personal monitoring should be used for non-industrial workers” (Ref. 1).

Air Sampling. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure to the CPE Cluster chemicals through air for workers in manufacturing, processing, industrial and non-industrial use facilities. EPA believes that a combination of modeled data and existing data (e.g., non-U.S. data for similar activities/scenarios) could be used to determine or predict effects on workers exposed to air containing the CPE Cluster chemicals in an industrial and non-industrial environment.

The CPE Problem Formulation and Initial Assessment document states that EPA’s lack of toxicity data for inhalation

and dermal routes of exposure as the basis for not further elaborating these exposure pathways. However, as described in Unit IV.C.1., EPA has described data and approaches that may be useful in filling these data gaps such that this may not be a critical data gap going forward. Additionally, the petitioners cited a report from the National Institute of Occupational Safety and Health (NIOSH) titled: “Assessment of Occupational Exposure to Flame Retardants” that aims to quantify and characterize occupational exposure routes (inhalation, ingestion, or dermal) for CPE Cluster chemicals as potentially useful for EPA to consider (Ref. 138). EPA agrees that this report appears to include a number of scenarios and measurements for which the petitioners are asking for testing and that EPA would consider any relevant information that results from this ongoing study. However, the petition fails to explain how it considered worker exposure or why a testing order under section 4 would be necessary for additional information.

If measured data are not available, it is still possible to assess exposure using modelling approaches. Specifically, EPA’s ChemSTEER could be used to estimate worker exposure under a number of manufacturing, processing and use scenarios (Ref. 126). In addition, EPA may be able to use air concentration information or an estimation approach for a structurally similar chemical to estimate work exposures under specific industrial or non-industrial scenarios. However, the petition does not address these possibilities, let alone explain why a testing order under section 4 would be necessary at this point. EPA considers these approaches to be reasonable to determine exposure to workers of manufacturing and processing facilities, but may decide to pursue targeted sampling in the future for workers in manufacturing and processing facilities to reduce uncertainty.

Dust Sampling. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure to the CPE Cluster chemicals through dust for workers in manufacturing, processing, industrial and non-industrial use facilities. EPA believes that a combination of modelling and existing data (e.g., non-U.S. data) could allow EPA to determine or predict effects on workers exposed to dust containing the CPE Cluster chemicals in an industrial and non-industrial environment.

EPA believes the approaches described earlier, Unit IV.C.4.b. and c.

regarding Air Sampling, are sufficient to characterize exposures to workers at manufacturing or processing facilities from exposure to dust. Sampling of settled dust (surface wipe and bulk sampling) using the OSHA Technical Manual (Ref. 139), as requested by the petitioners, may not be necessary. During Problem Formulation and Initial Assessment, EPA stated that inhalation and dermal exposure were the primary routes of occupational exposure for the CPE Cluster chemicals. Presence of the CPE Cluster chemicals in settled dust may indicate additional dermal and ingestion exposures are possible. However, surface wipe sampling does not provide a direct estimate of dermal or ingestion exposure. Surface wipe sampling would need to be combined with information on transfer efficiency between the surface, hands, and objects as well as the number of events to estimate exposures from ingestion (Ref. 140).

EPA notes that in the ongoing NIOSH study (Ref. 138) surface wipe sampling is not included, which provides support for the conclusion that settled dust is not a customary measure for occupational exposure. Furthermore, EPA would use any information generated from the NIOSH study considered relevant for this exposure pathway.

Biomonitoring. EPA believes the approaches described previously are sufficient to characterize exposures to workers at manufacturing or processing facilities from external doses/concentrations. The biomonitoring data collected following the protocols of the ongoing NIOSH study or other peer-reviewed studies, as requested by the petitioners, is not needed. EPA would, however, consider any data or information generated from the NIOSH study deemed to be relevant and applicable for discerning exposures from all exposure routes. *5. Exposures from recycling.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects to communities and workers specifically located at or near facilities that recycle the CPE Cluster chemical-containing products. EPA believes that the approaches requested by the petitioners to measure exposure to the CPE Cluster chemicals from recycling facilities may not be needed. These are the same approaches referenced in Unit IV.C.4.a.b. and c. EPA did not include in the Problem Formulation and Initial Assessment a search for data associated with the recycling of the CPE Cluster chemicals. Going forward, EPA would initiate a comprehensive search of

available data. EPA could then assess the nature of the data, including those cited by the petitioners (Refs. 141–143) to determine feasibility of conducting an assessment. For example, the following could inform development of exposure scenarios for recycling facilities within the United States:

- a. The number and location of recycling facilities in the United States;
- b. The types and volumes of products that are accepted by these sites; and
- c. the recycling and disposal methods employed at these facilities.

With such information, the recycling processes used in the U.S. could potentially be assessed. However, the petition does not address this possibility, let alone explain why a testing order under section 4 would be necessary on this point.

EPA also notes that the NIOSH study (Ref. 138) may inform occupational exposures from recycling facilities and could be considered in an occupational assessment of CPE Cluster chemicals. EPA also notes that the settled dust sampling and biomonitoring data, as requested by the petitioners, may not be the most appropriate data to collect for the reasons provided previously in Unit IV.C.4.b. and c. EPA would consider any data or information generated from the NIOSH study deemed to be relevant and applicable for discerning exposures from all exposure routes. 6. *Exposure from disposal.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects to communities and workers specifically located at or near facilities that dispose of CPE Cluster chemical-containing products. EPA believes that the approaches requested by the petitioners to measure exposure to the CPE Cluster chemicals from disposal facilities may not be needed. These are the same approaches referenced in Unit IV.C.4.a.b. and c. EPA did not include in the Problem Formulation and Initial Assessment a search for data associated with the disposal of the CPE Cluster chemicals. Going forward, EPA would initiate a comprehensive search of available data. EPA could then assess the nature of the data to determine feasibility of conducting an assessment. For example, the following could inform development of exposure scenarios for recycling facilities within the United States:

- a. The number and location of recycling facilities in the United States;
- b. The types and volumes of products that are accepted by these sites; and
- c. The recycling and disposal methods employed at these facilities.

With such data or information, the recycling processes used in the U.S. could potentially be assessed. However, the petition does not address this possibility, let alone explain why a testing order under section 4 would be necessary at this point.

EPA also notes that the NIOSH study (Ref. 138), may inform occupational exposures from disposal facilities and could be considered in an occupational assessment of the CPE Cluster chemicals. EPA also notes that the settled dust sampling and biomonitoring data, as requested by the petitioners, may not be the most appropriate data to collect for the reasons provided previously in Unit IV.C.4.b. and c., but that EPA would consider any data or information generated from the NIOSH study deemed to be relevant and applicable for discerning exposures from any/all exposure routes. 7. *Exposures of birds, wildlife and sediment organisms.*

Terrestrial organism toxicity. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict CPE Cluster chemicals' effects to terrestrial organisms. The avian toxicity test (OCSPP 850.2100: Avian Acute Oral Toxicity Test) (Ref. 144) as requested by the petitioners is not necessary. Although the Problem Formulation and Initial Assessment previously stated that there was limited ability to quantify risks because of a lack of monitoring data and hazard endpoints (Ref. 2), studies have been identified since the publication of the Problem Formulation and Initial Assessment document including a study by Fernie et al. (2013) measuring toxicity of all three CPE Cluster chemicals to American Kestrels (Ref. 145) using a modified Avian Dietary Toxicity Test (OCSPP 850.2200) (Ref. 146), and a study on the toxicity of TCEP to hens (Ref. 147).

EPA considers the three chemicals in the CPE Cluster to have similar hazard profiles from an ecological perspective and hence, read-across, in which data for one structurally similar chemical can be used to assess the toxicity of another, could be appropriately applied. EPA's conclusion regarding this approach is supported by its use in risk assessments performed by the European Union (Refs. 96, 97 and 148). Collectively, the available data could be used to determine or predict the effects of the CPE Cluster chemicals on terrestrial organism, specifically birds, from repeated exposures.

Furthermore, EPA's use of available existing toxicity information reduces the use of vertebrate animals in the testing

of chemical substances in a manner consistent with provisions described in TSCA section 4(h).

Soil/Sediment dwelling organisms. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict the CPE Cluster chemicals' effects to soil/sediment dwelling organisms. The Earthworm Subchronic Toxicity Test (OCSPP 850.3100) (Ref. 152) as requested by petitioners is not needed. Although the Problem Formulation and Initial Assessment states that data was not available to characterize risk for sediment dwelling organisms (Ref. 2), adequate sediment toxicity studies exist for TDCPP and this data could also be used to evaluate and characterize the effects of the other CPE Cluster chemicals to sediment dwelling organisms using read-across. There are chronic toxicity studies on three sediment-dwelling species, *Chironomus riparius* (midge), *Hyalella Azteca* (amphipod) and *Lumbriculus variegatus* (oligochaete) (Refs. 150–152). Since publication of the Problem Formulation and Initial Assessment, EPA identified additional data on soil/sediment dwelling organisms that could be used to assess risks to these organisms (Refs. 153–155).

EPA considers the three chemicals in the CPE Cluster to have similar hazard profiles from an ecological perspective and hence, read-across, in which data for one structurally similar chemical can be used to assess the toxicity of another, could be appropriately applied. EPA's conclusion regarding this approach is supported by its use in risk assessments performed by the European Union (Refs. 96, 97, and 148). Collectively, the available data could be used to determine or predict the effects of the CPE Cluster chemicals on soil/sediment dwelling organisms.

Plant toxicity. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict the CPE Cluster chemicals effects on plants. The Early Seedling Growth Toxicity Test (OCSPP 850.4230) (Ref. 156) as requested by the petitioners is not needed. Since publication of the Problem Formulation and Initial Assessment document, EPA identified data on the toxicity to terrestrial plants from TDCPP (Ref. 157), TCEP (Ref. 158) and TCPP (Ref. 159). The data could be used to determine or predict the effects of the CPE Cluster chemicals on plants.

8. *EPA's conclusions.* EPA denied the request to issue an order under TSCA section 4 because the TSCA section 21 petition does not set forth sufficient

facts for EPA to find that the information currently available to the Agency, including existing studies (identified prior to or after publication of EPA's Problem Formulation and Initial Assessment) on the CPE Cluster chemicals as well as alternate approaches for risk evaluation is insufficient to permit a reasoned determination or prediction of the health or environmental effects of the CPE Cluster chemicals at issue in the petition nor that the specific testing the petition identified is necessary to develop additional information, as elaborated throughout Unit IV. of this notice.

Furthermore, to the extent the petitioners request vertebrate testing, EPA emphasizes that future petitions should discuss why such testing is appropriate, considering the reduction of testing on vertebrates encouraged by TSCA section 4(h), as amended.

V. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

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List of Subjects in 40 CFR Chapter I

Environmental protection, Flame retardants, Hazardous substances, chlorinated phosphate ester cluster.

Dated: April 6, 2017.

Wendy Cleland-Hamnett, Acting,
Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

[FR Doc. 2017–07404 Filed 4–11–17; 8:45 am]

BILLING CODE 6560–50–P

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 64

[CG Docket Nos. 10–51 and 03–123; FCC 17–26]

Structure and Practices of the Video Relay Services Program

AGENCY: Federal Communications Commission.

ACTION: Proposed rule.

SUMMARY: In this document, the Commission seeks comment on establishing performance goals and service quality metrics to evaluate the efficacy of the video relay service (VRS) program and on the incidence of “phony” VRS calls and the handling of such calls. The Commission also proposes a four-year plan for VRS compensation and rule amendments to permit server-based routing of VRS and point-to-point video calls, provide safeguards regarding who may use VRS at enterprise and public videophones, allow customer service support centers to access the Telecommunications Relay Service (TRS) Numbering Directory for direct video calling, and make a technical change to per-call validation requirements. The Commission also seeks comment on whether to continue including research and development in the TRS Fund budget, prohibit non-service related inducements to register for VRS, and prohibit the use of non-compete provisions in VRS communications assistant (CA) employment contracts.

DATES: For VRS compensation rates, server-based routing, and research and development, comments are due April 24, 2017, and reply comments are due May 4, 2017. For performance goals and service quality metrics, the incidence and handling of “phony” VRS calls, VRS use of enterprise and public videophones, direct video calling customer support services, per-call validation procedures, non-service related inducements, and non-compete provisions in VRS employment contracts, comments are due May 30, 2017, and reply comments are due June 26, 2017.

ADDRESSES: You may submit comments, identified by CG Docket Nos. 10–51 and 03–123, by any of the following methods:

- **Electronic Filers:** Comments may be filed electronically using the Internet by accessing the Commission's Electronic Comment Filing System (ECFS), through the Commission's Web site <http://apps.fcc.gov/ecfs/>. Filers should follow the instructions provided on the Web

Appendix C.2: Tetrabromobisphenol A (TBBPA); TSCA Section 21 Petition

ENVIRONMENTAL PROTECTION AGENCY**40 CFR Part 300****[EPA-HQ-SFUND-1983-0002; FRL-9959-04-Region 4]****National Oil and Hazardous Substances Pollution Contingency Plan; National Priorities List: Deletion of the Perdido Ground Water Contamination Superfund Site****AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Proposed rule; notice of intent.

SUMMARY: The Environmental Protection Agency Region 4 is issuing a Notice of Intent to Delete the Perdido Ground Water Contamination Superfund Site (Site) located in Baldwin County, Alabama, from the National Priorities List (NPL) and requests public comments on this proposed action. The NPL, promulgated pursuant to section 105 of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980, as amended, is an appendix of the National Oil and Hazardous Substances Pollution Contingency Plan (NCP). The EPA and the State of Alabama, through the Alabama Department of Environmental Management (ADEM), have determined that all appropriate response actions under CERCLA have been completed. However, this deletion does not preclude future actions under Superfund.

DATES: Comments must be received by April 17, 2017.

ADDRESSES: Submit your comments, identified by Docket ID no. EPA-HQ-SFUND-1983-0002, by mail to Deborah P. Cox, PE, Remedial Project Manager, Superfund Restoration and Sustainability Branch, Superfund Division, U.S. Environmental Protection Agency, Region 4, 61 Forsyth Street SW., Atlanta, Georgia 30303-8960. Comments may also be submitted electronically or through hand delivery/courier by following the detailed instructions in the **ADDRESSES** section of the direct final rule located in the rules section of this **Federal Register**.

FOR FURTHER INFORMATION CONTACT: Deborah P. Cox, PE, Remedial Project Manager, Superfund Restoration and Sustainability Branch, Superfund Division, U.S. Environmental Protection Agency, Region 4, 61 Forsyth Street SW., Atlanta, Georgia 30303-8960, phone 404-562-8317, email: cox.deborah@epa.gov.

SUPPLEMENTARY INFORMATION: In the “Rules and Regulations” Section of today’s **Federal Register**, we are publishing a direct final Notice of Deletion of the Site without prior Notice of Intent to Delete because we view this as a noncontroversial revision and anticipate no adverse comment. We have explained our reasons for this deletion in the direct final Notice of Deletion, and those reasons are incorporated herein. If we receive no adverse comment(s) on this deletion action, we will not take further action on this Notice of Intent to Delete. If we receive adverse comment(s), we will withdraw the direct final Notice of Deletion, and it will not take effect. We will, as appropriate, address all public comments in a subsequent final Notice of Deletion based on this Notice of Intent to Delete. We will not institute a second comment period on this Notice of Intent to Delete. Any parties interested in commenting must do so at this time.

For additional information, see the direct final Notice of Deletion which is located in the *Rules* section of this **Federal Register**.

List of Subjects in 40 CFR Part 300

Environmental protection, Air pollution control, Chemicals, Hazardous waste, Hazardous substances, Intergovernmental relations, Penalties, Reporting and recordkeeping requirements, Superfund, Water pollution control, Water supply.

Authority: 33 U.S.C. 1321(c)(2); 42 U.S.C. 9601-9657; E.O. 12777, 56 FR 54757, 3 CFR, 1991 Comp., p. 351; E.O. 12580, 52 FR 2923; 3 CFR, 1987 Comp., p. 193.

Dated: September 6, 2016.

V. Anne Heard,*Acting Regional Administrator, Region 4.*

[FR Doc. 2017-05289 Filed 3-16-17; 8:45 am]

BILLING CODE 6560-50-P**ENVIRONMENTAL PROTECTION AGENCY****40 CFR Chapter I****[EPA-HQ-OPPT-2016-0770; FRL-9960-09]****Tetrabromobisphenol A (TBBPA); TSCA Section 21 Petition; Reasons for Agency Response****AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Petition; reasons for Agency response.

SUMMARY: This document provides the reasons for EPA’s response to a petition it received under the Toxic Substances Control Act (TSCA). The TSCA section

21 petition was received from Earthjustice, Natural Resources Defense Council, Toxic-Free Future, Safer Chemicals, Healthy Families, BlueGreen Alliance, and Environmental Health Strategy Center on December 13, 2016. The petitioners requested that EPA issue an order under TSCA section 4, requiring that testing be conducted by manufacturers (which includes importers) and processors on tetrabromobisphenol A (“TBBPA”) (CAS No. 79-94-7). After careful consideration, EPA denied the TSCA section 21 petition for the reasons discussed in this document.

DATES: EPA’s response to this TSCA section 21 petition was signed March 10, 2017.

FOR FURTHER INFORMATION CONTACT:

For technical information contact: Virginia Lee, Chemical Control Division (7405M), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460-0001; telephone number: (202) 564-4142; email address: lee.virginia@epa.gov.

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1404; email address: TSCA-Hotline@epa.gov.

SUPPLEMENTARY INFORMATION:**I. General Information***A. Does this action apply to me?*

This action is directed to the public in general. This action may, however, be of interest to those persons who are or may manufacture (which includes import) or process the chemical tetrabromobisphenol A (“TBBPA”) (CAS No. 79-94-7). Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. How can I access information about this petition?

The docket for this TSCA section 21 petition, identified by docket identification (ID) number EPA-HQ-OPPT-2016-0770, is available at <http://www.regulations.gov> or at the Office of Pollution Prevention and Toxics Docket (OPPT Docket), Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave. NW., Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone

number for the OPPT Docket is (202) 566-0280. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

II. TSCA Section 21

A. What is a TSCA section 21 petition?

Under TSCA section 21 (15 U.S.C. 2620), any person can petition EPA to initiate a rulemaking proceeding for the issuance, amendment, or repeal of a rule under TSCA section 4, 6, or 8 or an order under TSCA section 4 or 5(e) or (f). A TSCA section 21 petition must set forth the facts that are claimed to establish the necessity for the action requested. EPA is required to grant or deny the petition within 90 days of its filing. If EPA grants the petition, the Agency must promptly commence an appropriate proceeding. If EPA denies the petition, the Agency must publish its reasons for the denial in the **Federal Register**. A petitioner may commence a civil action in a U.S. district court to compel initiation of the requested rulemaking proceeding within 60 days of either a denial or the expiration of the 90-day period.

B. What criteria apply to a decision on a TSCA section 21 petition?

1. *Legal standard regarding TSCA section 21 petitions.* Section 21(b)(1) of TSCA requires that the petition “set forth the facts which it is claimed establish that it is necessary” to issue the rule or order requested. 15 U.S.C. 2620(b)(1). Thus, TSCA section 21 implicitly incorporates the statutory standards that apply to the requested actions. Accordingly, EPA has relied on the standards in TSCA section 21 and in the provisions under which actions have been requested to evaluate this TSCA section 21 petition. In addition, TSCA section 21 establishes standards a court must use to decide whether to order EPA to initiate rulemaking in the event of a lawsuit filed by the petitioner after denial of a TSCA section 21 petition. 15 U.S.C. 2620(b)(4)(B).

2. *Legal standard regarding TSCA section 4 rules.* EPA must make several findings in order to issue a rule or order to require testing under TSCA section 4(a)(1)(A)(i). In all cases, EPA must find that information and experience are insufficient to reasonably determine or predict the effects of a chemical substance on health or the environment and that testing of the chemical substance is necessary to develop the missing information. 15 U.S.C. 2603(a)(1). In addition, EPA must find that the chemical substance may present an unreasonable risk of injury under

section 4(a)(1)(A)(i). Id. If EPA denies a petition for a TSCA section 4 rule or order and the petitioners challenge that decision, TSCA section 21 allows a court to order EPA to initiate the action requested by the petitioner if the petitioner demonstrates to the satisfaction of the court by a preponderance of the evidence in a *de novo* proceeding that findings very similar to those described in this unit with respect to a chemical substance have been met.

III. Summary of the TSCA Section 21 Petition

A. What action was requested?

On December 13, 2016, Earthjustice, Natural Resources Defense Council, Toxic-Free Future, Safer Chemicals, Healthy Families, BlueGreen Alliance, and Environmental Health Strategy Center petitioned EPA to issue an order under TSCA section 4(a)(1), 90 days after the petition was filed, requiring that testing be conducted by manufacturers (which includes importers) and processors on tetrabromobisphenol A (“TBBPA”) (CAS No. 79-94-7) (Ref. 1).

B. What support do the petitioners offer?

The petitioners state section 4(a)(1) of TSCA requires EPA to direct testing on a chemical substance or mixture if it finds the following criteria are met:

1. The manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment.
2. There is insufficient information and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture, or of any combination of such activities on health or the environment can reasonably be determined or predicted.
3. Testing is necessary to develop such information.

The petitioners assert that TBBPA “may present an unreasonable risk of injury to health or the environment” because there is substantial evidence that TBBPA may be toxic, including conclusions from:

- EPA’s TSCA Work Plan Chemical Problem Formulation and Initial Assessment (Ref. 2), which states TBBPA “can be considered hazardous to the environment” and that “there is some concern” for certain cancers and developmental effects.
- The International Agency for Research on Cancer (IARC) has identified TBBPA as probably carcinogenic to humans (Ref. 3).

- Multiple *in vitro* and animal tests, where TBBPA has been detected to cause endocrine effects, reproductive effects, neurological effects, and immunological effects (Refs. 4–9).

The petitioners also note that EPA, upon adding TBBPA in 1999 to the Toxics Release Inventory (TRI) established under the Emergency Planning and Community Right to Know Act, concluded that “TBBPA is toxic” because “[i]t has the potential to kill fish, daphnid, and mysid shrimp, among other adverse effects, based on chemical and/or biological interactions.” 64 FR 58666, 58708. The petitioners assert there is TBBPA exposure to humans and the environment based on the following conclusions.

- TBBPA has the highest production volume of any brominated flame retardant and is extensively used in consumer products, including children’s products (Ref. 2). The potential for widespread exposure is extremely high.
 - In 2012, TRI indicated that 127,845 pounds of TBBPA were released into the environment (Ref. 2). Such releases indicate the potential for widespread exposure in the population.
 - The presence of TBBPA in people and the environment (biota and environmental media) is established and affirmed in EPA’s TBBPA Problem Formulation and Initial Assessment (Ref. 2).
- With the evidence of toxicity and exposure and EPA’s addition of TBBPA to TRI (Ref. 10), the petitioners argue that TBBPA clearly meets the TSCA section 4 criteria for “may present an unreasonable risk of injury to health or the environment.”

The petitioners also assert there is “insufficient information” on TBBPA based on EPA’s TBBPA Problem Formulation (Ref. 2), which petitioners say cited lack of data for:

- Dermal and inhalation exposures, diet and drinking water exposures, exposures to communities near facilities that manufacture and process TBBPA, exposures to communities near facilities where “e-waste” is disposed of and recycled, exposures to the workers in manufacturing, processing, disposal and recycling facilities, and exposures to degradation and combustion products.
- developmental, reproductive and neurological toxicity, endocrine disruption, and genotoxic effects.

The petitioners argue that the testing recommended in the petition is critical to address this allegedly insufficient information and for performing any TSCA section 6 risk evaluation of TBBPA, and they request EPA to not

commence the risk evaluation for TBBPA until data generated to comply with the section 4 test order requested by the petitioners have been received by EPA.

IV. Disposition of TSCA Section 21 Petition

A. What was EPA's response?

After careful consideration, EPA has denied the petition. A copy of the Agency's response, which consists of two letters to the signatory petitioners from Earthjustice and Natural Resources Defense Council (Ref. 11), is available in the docket for this TSCA section 21 petition.

B. Background Considerations for the Petition

EPA published a Problem Formulation and Initial Assessment for TBBPA in August 2015 (Ref. 2). As stated on EPA's Web site titled "Assessments for TSCA Work Plan Chemicals" (Ref. 12), "As a first step in evaluating TSCA Work Plan Chemicals, EPA performs problem formulation to determine if available data and current assessment approaches and tools will support the assessments." During development of the Problem Formulation and Initial Assessment document for TBBPA, EPA followed an approach developed for assessing chemicals under TSCA as it existed at that time.

Under TSCA prior to the June amendments, EPA performed risk assessments on individual uses, hazards, and exposure pathways. The approach taken during the TSCA Work Plan assessment effort was to focus risk assessments on those conditions of use that were most likely to pose concern, and for which EPA identified the most robust readily available, existing, empirical data, located using targeted literature searches, although modeling approaches and alternative types of data were also considered. EPA relied heavily on previously conducted assessments by other authoritative bodies and well-established conventional risk assessment methodologies in developing the Problem Formulation documents. Although EPA identified existing data and presented them in the problem formulations, EPA did not necessarily undertake a comprehensive search of available data or articulate a range of scientifically supportable approaches that might be used to perform risk assessment for various uses, hazards, and exposure pathways in the absence of directly applicable, empirical data prior to seeking public input. Rather,

EPA generally elected to focus its attention on the uses, hazards, and exposure pathways that appeared to be of greatest concern and for which the most extensive relevant data had been identified. (Ref. 2).

As EPA explains on its Web site, "Based on on-going experience in conducting TSCA Work Plan Chemical assessments and stakeholder feedback, starting in 2015 EPA will publish a problem formulation for each TSCA Work Plan assessment as a stand-alone document to facilitate public and stakeholder comment and input prior to conducting further risk analysis. Commensurate with release of a problem formulation document, EPA will open a public docket for receiving comments, data or information from interested stakeholders. EPA believes publishing problem formulations for TSCA Work Plan assessments will increase transparency of EPA's thinking and analysis process, provide opportunity for public/stakeholders to comment on EPA approach and provide additional information/data to supplement or refine assessment approach prior to EPA conducting detailed risk analysis and risk characterization." (Ref. 12).

EPA's 2015 Problem Formulation and Initial Assessment for TBBPA does not constitute a full risk assessment for TBBPA, nor does it purport to be a final analysis plan for performing a risk assessment or to present the results of a comprehensive search for available data or approaches for conducting risk assessments. Rather, it is a preliminary step in the risk assessment process, which EPA desired to publish to provide transparency and the opportunity for public input. EPA received comments from Earthjustice, Natural Resources Defense Council and others during the public comment period, which ended in November 2015 (Ref. 13). After the public comment period, EPA was in the process of considering this input in refining the analysis plan and further data collection for conducting a risk assessment for TBBPA.

On June 22, 2016, Congress passed the Frank R. Lautenberg Chemical Safety for the 21st Century Act. EPA has interpreted the amended TSCA as requiring that forthcoming risk evaluations encompass all manufacturing, processing, distribution in commerce, use, and disposal activities that the Administrator determines are intended, known, or reasonably foreseen (Ref. 14). This interpretation, encompassing "conditions of use" as defined by TSCA section 3(4), has prompted EPA to re-

visit the scoping and problem formulation for risk assessments under TSCA. Other provisions included in the amended TSCA, including section 4(h) regarding alternative testing methods, have also prompted EPA to evolve its approach to scoping and conducting risk assessments. The requirement to consider all conditions of use in risk evaluations—and to do so during the three to three and a half years allotted in the statute—has led EPA to more fully evaluate the range of data sources and technically sound approaches for conducting risk evaluations. Thus, a policy decision articulated in a problem formulation under the pre-amendment TSCA not to proceed with risk assessment for a particular use, hazard, or exposure pathway does not necessarily indicate at this time that EPA will need to require testing in order to proceed to risk evaluation. Rather, such a decision indicates an area in which EPA will need to further evaluate the range of potential approaches—including generation of additional test data—for proceeding to risk evaluation. EPA is actively developing and evolving approaches for implementing the new provisions in amended TSCA. These approaches are expected to address many, if not all, of the data needs asserted in the petition. Whereas under the Work Plan assessment effort, EPA sometimes opted not to include conditions of use for which data were limited or lacking, under section 6 of amended TSCA, EPA will evaluate all conditions of use and will apply a broad range of scientifically defensible approaches—using data, predictive models, or other methods—that are appropriate and consistent with the provisions of TSCA section 26, to characterize risk and enable the Administrator to make a determination of whether the chemical substance presents an unreasonable risk.

C. What was EPA's reason for this response?

For the purpose of making its decision on the response to the petition, EPA evaluated the information presented or referenced in the petition and its authority and requirements under TSCA sections 4 and 21. EPA also evaluated relevant information that was available to EPA during the 90-day petition review period that may have not been available or identified during the development of EPA's TBBPA Problem Formulation and Initial Assessment (Ref. 2).

EPA agrees that the manufacture, distribution in commerce, processing, use, or disposal of TBBPA may present an unreasonable risk of injury to health

or the environment under TSCA section 4(a)(1)(A). EPA also agrees that the Problem Formulation and Initial Assessment was not comprehensive in scope with regard to the conditions of use of TBBPA, exposure pathways/routes, or potentially exposed populations. However, the Problem Formulation and Initial Assessment was not designed to be comprehensive. Rather, the Problem Formulation and Initial Assessment was developed under EPA's then-existing process, as explained previously. It was a fit-for-purpose document to meet a TSCA Work Plan (*i.e.*, pre-Lautenberg Act) need. Going forward under TSCA, as amended, EPA will conform its analyses to TSCA, as amended. EPA has explained elsewhere how the Agency proposes to conduct prioritization and risk evaluation going forward (Refs. 15 and 16). However, EPA does not find that the petitioners have demonstrated, for each exposure pathway and hazard endpoint presented in the petition, that the existing information and experience available to EPA are insufficient to reasonably determine or predict the effects on health or the environment from "manufacture, distribution in commerce, processing, use, or disposal" of TBBPA (or any combination of such activities) nor that the specific testing they have identified is necessary to develop such information.

The discussion that follows provides the reasons for EPA's decision to deny the petition based on the finding for each requested test that the information on the individual exposure pathways and hazard endpoints identified by the petitioners does not demonstrate that there is insufficient information upon which the effects of TBBPA can reasonably be determined or predicted or that the requested testing is necessary to develop additional information. The sequence of EPA's responses follows the sequence in which requested testing was presented in the petition (Ref. 1).

1. *Dermal and Inhalation Exposure Toxicity. a. Dermal toxicity.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects to health from dermal exposure to TBBPA. Therefore, the toxicokinetics test (Organisation for Economic Co-operation (OECD) Test Guideline 417) (Ref. 17) via the dermal route and the skin absorption: In vivo test (OECD Test Guideline 427) (Ref. 18), requested by the petitioners, are not needed. The information already available includes oral toxicity studies and oral toxicokinetic studies identified in EPA's Problem Formulation and Initial

Assessment document (Ref. 2) and the dermal toxicokinetics study identified by the petitioners (Ref. 19). These available studies are sufficient to reasonably determine the internal doses of TBBPA for purposes of route-to-route (oral to dermal) extrapolation. The 2016 Yu et al. study, cited in the petition (Ref. 1), characterizes absorption and elimination, while distribution and metabolism characterization is available from studies using intravenous dosing (Ref. 20). Furthermore, the available studies do not indicate differential distribution, metabolism, and elimination specific to skin. Therefore, the dermal toxicokinetics study requested by the petitioners is not needed to inform or refine evaluation of dermal exposures.

b. Inhalation toxicity. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects to health from inhalation exposure to TBBPA. Therefore, the toxicokinetics test (OECD Test Guideline 417) (Ref. 17) via the inhalation route, requested by the petitioners, is not needed. As described in EPA's Problem Formulation and Initial Assessment (Ref. 2), EPA will use an alternative approach to evaluate risks from inhalation exposure to TBBPA. Because TBBPA is a solid, it may be reasonably predicted that particulates in the air are the primary form of TBBPA that would be inhaled. TBBPA particles in air that are inhaled are subsequently swallowed via the mucociliary escalator (Ref. 21). Once the particles are in the gastrointestinal tract, absorption can reasonably be assumed to be the same as in the oral toxicity studies and hence, oral toxicity studies can be used for risk assessment. Information is also available to estimate bioaccessibility of TBBPA from dust using an extraction test with an in vitro colon (Ref. 22). This additional information could also be considered when evaluating risks from TBBPA via the oral route. This approach would not require conducting the requested toxicokinetics test (Ref. 17).

Although a small percent of TBBPA particles may be in the respirable range and may be absorbed directly through the lungs, existing tests show that no systemic effects were observed in a 14-day inhalation toxicity study (Ref. 23). Therefore, EPA considers that assuming all inhaled particles are eventually swallowed and using existing oral toxicity data should not underestimate effects from inhaling TBBPA particles and therefore would reasonably predict such effects.

Furthermore, EPA's use of available existing toxicity information reduces the

use of vertebrate animals in the testing of chemical substances in a manner consistent with provisions described in TSCA section 4(h).

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects to the environment, specifically, toxicity to plants exposed to TBBPA via the air. Therefore, the early seedling growth toxicity test (OCSPP Test Guideline 850.4230) (Ref. 24), requested by the petitioners, is not needed. As previously mentioned, because TBBPA is a solid, it may be reasonably predicted that particulates in the air are the primary form of TBBPA that would exist in air. Furthermore, as stated on page 88 of EPA's Problem Formulation and Initial Assessment document (Ref. 2), "[u]ltimately air releases of TBBPA would be expected to undergo deposition to terrestrial and aquatic environments . . ." and "TBBPA tends to partition to soil and sediment . . .". These fate pathways for TBBPA are also shown in Figure 2–1 of EPA's Problem Formulation and Initial Assessment document (Ref. 2). Hence, exposure of plants to TBBPA is expected to occur primarily via soil and sediments after deposition from air, which is why EPA excluded this pathway from further assessment (Ref. 2, page 42), although EPA in the Problem Formulation and Initial Assessment document mistakenly mentioned plants in another sentence addressing "[e]xposure via *directly inhaling* [emphasis added] TBBPA," even though direct inhalation is not applicable to plants and thereby may have caused potential confusion to readers. If toxicity of TBBPA to plants were to be included in an assessment, toxicity data following exposure via soil and/or sediment exposures, not air, would be the scientifically relevant data needed. To this end, as described in EPA's Problem Formulation and Initial Assessment (Ref. 2), existing data and information on phytotoxicity of TBBPA to six plant species is available (Ref. 25). EPA's Problem Formulation and Initial Assessment document (Ref. 2) included references for and a brief description of the existing plant toxicity data (page 105). While assessment of soil-dwelling organisms is included in EPA's Problem Formulation and Initial Assessment document (Ref. 2), as depicted in Figure 2–1 and described on page 40, EPA indicated that the environmental risk assessment for the soil exposure pathway would be based on concentrations of concern derived from data for soil invertebrates (Ref. 2; Figure 2–1; Table 2–6; Page 40). Support for

EPA's selection of using species that are expected to be more sensitive to potential effects of TBBPA in soil is provided in EPA's summary of plant toxicity data, which states "... TBBPA is two to three orders of magnitude less toxic to terrestrial plants than to soil-dwelling organisms" (Ref. 2; Table_Apx F-2 and text on page 106).

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict toxicity of TBBPA to avian species. Hence, inhalation toxicokinetic studies (OECD Test Guideline 417) (Ref. 17) and the acute inhalation toxicity study (OCSP Test Guideline 870.1300) (Ref. 26) modified for birds, requested by the petitioners, are not needed. Although the Problem Formulation and Initial Assessment document states, "Exposure via directly inhaling TBBPA will not be assessed because no information is available on the toxicity of tetrabromobisphenol A to plants and other wildlife organisms (e.g., birds) exposed via the air." (Ref. 2; page 42), EPA's primary rationale for not including further elaboration of inhalation risks to avian species, as discussed in the Problem Formulation and Initial Assessment document (Ref. 2; page 32 and Appendix F) is TBBPA's low avian toxicity demonstrated in existing studies.

Halldin et al., 2001 and Berg et al., 2001 (Refs. 27 and 28) indicate no effects to egg-laying female quail nor embryos (except at very high doses). The Halldin et al. (Ref. 27) study also included toxicokinetic data indicating that TBBPA is rapidly metabolized and excreted in birds (both embryos and egg-laying females). In these studies, TBBPA was delivered by intravenous injection into females and direct injection into eggs. This dosing regimen assures full (100%) delivery of the dose into the animal, which does not occur in nature, and thus provides the most sensitive means to detect the toxicity of the TBBPA. Other routes of exposure (*i.e.*, oral, inhalation, dermal) result in incomplete absorption limiting the systematic availability of TBBPA compared to the intravenous injection (*i.e.*, less than 100% delivered dose). Hence, intravenous toxicity test designs provide a good understanding of the potential toxicity (or lack thereof) of a chemical. In addition to the low avian toxicity of TBBPA, demonstrated via intravenous injection, inhalation is not expected to be a substantial exposure pathway to wildlife for TBBPA (Refs. 29 and 30). The predominant route of exposure to terrestrial wildlife for a chemical with physical-chemical

properties (*i.e.*, Log K_{ow} = 5.90; water solubility = 4.16 mg/L) and partitioning parameters (*i.e.*, low mobility in soil) such as TBBPA is not expected to be via inhalation, but rather through ingestion because the TBBPA will predominantly partition to soils and sediments if/when released to the environment. The physical-chemical properties of TBBPA also indicate that the fate of TBBPA into water would result in preferential partitioning into sediments and biota (fish or other aquatic organism). Available monitoring data support this conclusion, with higher concentrations of TBBPA in soil and fish relative to concentrations in air.

Hence, additional toxicokinetic studies by the inhalation route is not needed to conduct a reasoned determination or prediction of TBBPA risk to birds.

Furthermore, EPA's use of available existing toxicity information reduces the use of vertebrate animals in the testing of chemical substances in a manner consistent with provisions described in TSCA section 4(h).

2. Diet and Drinking Water Exposures.

a. *Diet.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure to TBBPA via diet. Testing of food products for TBBPA contamination, such as the plant uptake and translocation test (OCSP Test Guideline 850.4800) (Ref. 31) and modified methods for TBBPA using the Food & Drug Administration's (FDA) Drug & Chemical Residues Methods (Ref. 32), requested by the petitioners, is not necessary because existing data are available to address this exposure pathway.

While a plant uptake study combined with soil concentrations could be used to estimate dietary exposures from plants, chemicals with low water solubility and higher log K_{ow} values similar to TBBPA are less likely to bioaccumulate in plants compared to other foods, such as meats, fish and dairy products (Ref. 33). Hence, other food items, such as meats, fish and dairy products would be expected to be primary contributors to dietary exposures. Available market basket surveys for TBBPA support this, with most samples comprised of lipid-rich food groups (Ref. 34). There were 465 food samples collected in Europe between 2003 and 2010. Most of these were comprised of lipid-rich food groups; however, some vegetable and grain based food groups were sampled. All samples from this study were below the level of quantification, which was approximately <1 ng/g wet weight,

although this varied by food group (Ref. 35). To address dietary exposure from TBBPA, EPA could use a combination of approaches. First, there are existing plant uptake studies available that could be used to estimate TBBPA concentrations in plants from modeled or measured near-facility soil concentrations (Refs. 36 and 37). These studies are not cited in the petition. This approach is supported by a study, that EPA identified since the Problem Formulation and Initial Assessment document was published, that compared a wide variety of plant uptake studies with available models that estimate soil to plant uptake (Ref. 38). Any modeled estimate can be compared to available measured data and a range of values informed by both approaches could be derived. EPA could model soil concentrations from TRI data; these concentrations along with available physical-chemical properties can be used to reasonably estimate plant concentrations and associated dietary exposures. There is also an existing study that quantified soil and plant TBBPA concentrations near a facility (Ref. 39). This data can be used to supplement and/or evaluate the modeling approach. Because existing approaches exist for estimating plant concentrations of TBBPA (modeling and market basket data), the plant uptake and translocation test (Ref. 31) is not necessary.

EPA recognizes that dietary exposures come from a wide variety of sources, not just plants. Market basket surveys provide food concentrations, which can be used to estimate dietary exposure. There are market basket surveys from other countries that measured TBBPA in various food products (Refs. 40 to 42). Other studies are available that provide data on TBBPA concentrations in breast milk or edible fish (Refs. 43 to 48). Fish concentrations can also be estimated from combining modeled or measured surface water concentrations with bioaccumulation/bioconcentration factors (BAF/BCF). Ingestion from other dietary sources, in addition to fish, shellfish, and breast milk (dairy, meat, fruits and vegetables and grains), can be estimated individually and in total using existing data. It is expected that ingestion of foods with higher lipid content, such as fish and milk, will contribute more to dietary exposure (Ref. 49) than other foods, such as plants. Levels may vary based on proximity to point sources when compared to levels detected in market basket surveys, and this can be considered in developing exposure scenarios and/or background estimates.

b. Drinking Water. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from exposure to TBBPA via drinking water. Sampling of waters in the vicinity of representative manufacturing and processing facilities known to discharge TBBPA, requested by the petitioners, is not necessary because an existing approach is available to address this exposure pathway.

EPA can use release data collected under EPA's TRI program to characterize TBBPA concentrations in surface water near TBBPA manufacturing and processing facilities.

In addition, while there are no data on TBBPA concentrations in finished drinking water, EPA can use surface water monitoring data as a surrogate for finished drinking water to assess potential risks posed by drinking TBBPA-contaminated water. EPA's Office of Water routinely derives Ambient Water Quality Criteria for the Protection of Human Health (Ref. 50) using the assumption that people may ingest surface water as a drinking water source over a lifetime. There are existing data on TBBPA concentrations in surface water to conduct a drinking water exposure assessment using surface water as a surrogate (Refs. 51 to 53).

EPA believes these approaches are adequate, and likely conservative, to assess potential exposures to drinking water. First, the physical-chemical and fate properties of TBBPA, such as high sorption, low water solubility, and high K_{OC} indicate that concentrations of TBBPA in drinking water would be expected to be low prior to treatment. When sediment monitoring data is used with assumptions about K_{OC} , organic content, and density of water and sediment, surface water concentrations can be estimated to be generally low, below the highest levels reported in surface water (Refs. 54 to 56). This is supported by existing surface water monitoring data indicating the highest concentration of TBBPA in surface water is 4.87 ug/L with most data below 1 ug/L (Refs. 57 and 58). These same chemical and fate properties would indicate that drinking water treatment processes would further reduce TBBPA concentrations in finished drinking water. Overall, the contribution to exposure to TBBPA via drinking water is expected to be minimal.

3. Exposure from Manufacturing and Processing. a. Communities. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to

reasonably determine or predict exposure to TBBPA to communities near manufacturing and processing facilities. Air sampling, using methods, such as EPA Air Method Toxic Organics-9A (TO-9A, Determination Of Polychlorinated, Polybrominated And Brominated/Chlorinated Dibenzo-p-Dioxins And Dibenzofurans In Ambient Air) (Ref. 60), sampling of soils, and sampling of waters in the vicinity of representative manufacturing and processing facilities known to discharge TBBPA, as requested by the petitioners, is not necessary because EPA could use an alternative approach to evaluate exposure to TBBPA to communities near manufacturing and processing facilities. EPA could use release data collected under EPA's TRI program and a Gaussian dispersion model, such as AERMOD, to quantify air concentrations and air deposition to soil, to water bodies and to sediments near manufacturing and processing facilities. AERMOD is an EPA model that has been extensively reviewed and validated based on comparisons with monitoring data (Ref. 60). Variability and uncertainty associated with variable emission rates and degradation over time can also be characterized using modeling approaches whereas one-time or limited sampling cannot provide temporal characterizations. In addition, EPA can use monitoring data from other countries as surrogate "near-facility" monitoring data along with modeled estimates. However, the petition does not address this possibility, let alone explain why a testing order under section 4 would be necessary on this point. There are several references with sampling locations near facilities that can be considered, many of which were cited in the Problem Formulation and Initial Assessment document (Ref. 2). EPA considers this approach to be reasonable to determine exposure to communities near manufacturing or processing facilities, but may decide to pursue targeted sampling in the future near manufacturing and processing facilities to reduce uncertainty.

b. Workers. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict exposure to TBBPA to workers in manufacturing and processing facilities.

Since publication of the Problem Formulation and Initial Assessment document, EPA identified exposure monitoring data for Europe, China and the United States for several industries (the manufacture of epoxy resins and laminates; manufacture of printed circuit boards; and compounding of

acrylonitrile butadiene styrene (ABS resin) (Refs. 61 to 66).

As discussed previously, EPA is actively developing or evolving approaches for implementing the new provisions in amended TSCA. One such approach is to perform systematic literature reviews to identify and/or develop additional available data and modeling approaches for estimating worker inhalation exposure. EPA may also assess exposure concentration in the case of conversion of compounded ABS resin to finished products based on available monitoring data for other industries, such as manufacture of epoxy resins and laminates and manufacture of printed circuit boards. Furthermore, the National Institute of Occupational Safety and Health (NIOSH) has initiated a study titled: "Assessment of Occupational Exposure to Flame Retardants" that aims to quantify, characterize occupational exposure (inhalation, ingestion, or dermal) among workers, and to compare workers' exposures to those of the general population (Ref. 67). Data generated from the NIOSH study is expected to inform occupational exposures and will be considered in an occupational assessment of TBBPA. However, the petition fails to explain how it considered these points or why a testing order under section 4 would be necessary for additional information.

EPA considers the approach considered in the previous paragraph to be reasonable to determine exposure to workers in manufacturing and processing facilities, but may decide to pursue targeted sampling in the future near manufacturing and processing facilities to supplement or refine these approaches.

Dust. EPA believes the approaches described earlier in this unit are sufficient to characterize exposures to workers at manufacturing or processing facilities from external doses/concentrations. Sampling of settled dust (surface wipe and bulk sampling) using the OSHA Technical Manual (Ref. 68), as specifically requested by the petitioners, is not needed. Presence of TBBPA in settled dust may indicate additional dermal and ingestion exposures are possible. However, surface wipe sampling does not provide a direct estimate of dermal or ingestion exposure. Surface wipe sampling would need to be combined with information on transfer efficiency between the surface, hands, and objects, as well as the number of events to estimate exposures from ingestion (Ref. 69). EPA notes that in the NIOSH study that is in progress surface wipe sampling is not included, which provides support for

the conclusion that settled dust is not a customary measure for occupational exposure. EPA would, however, use any information generated from the NIOSH study considered relevant for this exposure pathway.

Biomonitoring. EPA believes the approaches described previously are sufficient to characterize exposures to workers at manufacturing or processing facilities from external doses/concentrations. Therefore, the biomonitoring data collected following the protocols of the current NIOSH study, as requested by the petitioners, is not needed. EPA would, however, consider any data or information generated from the NIOSH study deemed to be relevant and applicable for discerning exposures from any/all exposure routes.

4. *Exposure from recycling.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict communities specifically located at or near and workers in facilities that recycle TBBPA-containing products. In the Problem Formulation and Initial Assessment document (Ref. 2), EPA identified three monitoring studies that describe concentrations of TBBPA in soil, sediment, and sludge near manufacturing and recycling facilities (Refs. 71, 72, 76). Since publication of the Problem Formulation and Initial Assessment document (Ref. 2), EPA has identified four monitoring studies that describe concentrations of TBBPA in soil, sediment, indoor and outdoor dust from sampling locations in and near e-waste recycling facilities in other countries (Refs. 70, 73 to 75). These data may be useful for estimating exposures at or near U.S. recycling facilities.

However, EPA intends to further assess how comparable the nature and magnitude of these types of facilities and handling of TBBPA-containing products are to facilities within the U.S. EPA may collect available information related to estimating potential extent and magnitude of exposure. For example, the following could inform development of exposure scenarios for recycling facilities within the United States:

- a. The number and location of recycling facilities in the United States,
- b. the types and volumes of products that are accepted by these sites, and
- c. the recycling and disposal methods employed at these facilities.

With such data or information, the recycling processes used in the U.S. could be compared with the processes used in the studies characterizing the foreign facilities. However, the petition

does not address this possibility, let alone explain why a testing order under section 4 would be necessary on this point. If the processes are similar, EPA could extrapolate from foreign facilities to U.S. facilities. If EPA determines these previously indicated approaches are not reasonable to determine exposures, then sampling of soils, sediments and waters in the vicinity of facilities and air to which workers may be exposed at facilities known to recycle TBBPA-containing products, as requested by the petitioners, may become necessary. EPA also notes that the NIOSH study, "Assessment of Occupational Exposure to Flame Retardants," (Ref. 67) may inform occupational exposures from recycling facilities and will be considered in an occupational assessment of TBBPA. EPA also notes that the settled dust sampling and biomonitoring data, as requested by the petitioners, may not be the most appropriate data to collect for the reasons provided previously in Unit IV.C.3.b., but that EPA would consider any data or information generated from the NIOSH study deemed to be relevant and applicable for discerning exposures from any/all exposure routes.

5. *Exposure from disposal. a. Landfills, wastewater treatment plants, and sewage sludge.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict movement of TBBPA from landfills in soil columns. Leaching studies (OCSPP Testing Guideline 835.1240) (Ref. 77), requested by the petitioners, are not necessary because an existing approach is available to address this fate pathway. Studies measuring the sorption of TBBPA to soil, sand columns, and sediment are available as discussed in Appendix C of the Problem Formulation and Initial Assessment document (Ref. 2). Larsen et al. (2001) reported negligible leaching potential of TBBPA applied to soil and sand columns. (Ref. 78). The adsorption of TBBPA to sediment has been reported (Ref. 79) and suggest low mobility in soil and partitioning to sediments. Data from these existing studies can also serve as input to soil transport models to estimate mobility.

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict transformation processes of TBBPA, which would be episodically and/or continuously released to wastewater. The simulation tests to assess the primary and ultimate biodegradability of chemicals discharged to wastewater

(OPPTS Test Guideline 835.3280) (Ref. 80), requested by the petitioners, is not needed because primary degradation and major transformation products can be determined from existing studies on the ultimate biodegradability of TBBPA in aerobic and anaerobic sludge. One of the studies (Ref. 81) was discussed in Appendix C of EPA's Problem Formulation and Initial Assessment (Ref. 2). Two additional studies (Refs. 82 and 83) were identified after publication of EPA's document (Ref. 2). Li, et al. (2015) (Ref. 82) studied TBBPA transformation in nitrifying activated sludge (NAS). TBBPA transformation was accompanied by mineralization. Twelve metabolites, including those with single benzene ring, O-methyl TBBPA ether, and nitro compounds, were identified during the study. Potvin et al. (2012) (Ref. 83) measured the removal of TBBPA from influent to conventional activated sludge, submerged membrane and membrane aerated biofilm reactors. Removal of TBBPA from these wastewater treatment systems was found to be due to a combination of adsorption and biological degradation. Nyholm, et al. 2010 (Ref. 81) reported transformation as biodegradation half-lives for TBBPA in aerobic activated sludge, aerobic digested sludge, and anaerobic activated sludge amended soils.

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict effects from dietary exposure to crops where TBBPA contaminated sewage sludge is applied. A plant uptake and translocation test (OCSPP Test Guideline 850.4800) (Ref. 31), requested by the petitioners, is not necessary because existing data are available to address this fate pathway. As explained in the dietary exposure section, there are existing plant uptake studies available (Refs. 36 and 37). These data are also available to be used to estimate plant concentrations of agricultural crops where TBBPA-containing sewage sludge is applied. While a plant uptake study combined with sewage sludge concentrations could be used to estimate dietary exposures from plants, chemicals with low water solubility and higher log K_{ow} values similar to TBBPA, are less likely to bioaccumulate in plants compared to other foods, such as meats, fish and dairy products (Ref. 33). Hence, other food items, such as meats, fish and dairy products, would be expected to be primary contributors to dietary exposures. Available market basket surveys for TBBPA support this, with most samples comprised of lipid-

rich food groups (Ref. 34). To address dietary exposure from TBBPA, EPA could use a combination of approaches as described in the dietary exposure section. EPA believes this approach can provide a reasonable estimate of plant concentrations of agricultural crops grown where TBBPA-containing sewage sludge was applied.

b. Incineration. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict communities specifically located near facilities that incinerate TBBPA or TBBPA-containing products.

Electronic waste can be sent to waste-to-energy incinerators (Ref. 84). EPA's Problem Formulation and Initial Assessment for TBBPA (Ref. 2) included a study that measured TBBPA emissions (0.008 ng/L to air) from a mixed household and commercial waste incinerator in Japan (Ref. 85). These data may be useful for estimating exposures at or near U.S. facilities that incinerate TBBPA or TBBPA-containing products.

EPA intends to further assess these facilities and could use an approach that combines existing data to estimate the amount of combustion products at incineration facilities that could have formed from incinerating products that contain TBBPA. Such an approach could combine information on:

i. The types of by-products using data from EU (2006) (Ref. 62) and U.S. EPA (Ref. 87);

ii. information regarding types of consumer waste that contains TBBPA and may be sent to incinerators;

iii. information on the concentrations of TBBPA in various types of consumer waste; some of these data are available (Refs. 86 to 91);

iv. Toxics Release Inventory data on emissions of the dioxin, furan and polycyclic aromatic hydrocarbons (PAH) by-products from incinerators.

The emissions of dioxins, furans and PAHs could then be modeled using EPA's AERMOD air dispersion model (Ref. 60) and the amount of these by-products that might be attributed to TBBPA could be determined.

Another approach that EPA could take is to estimate exposures near facilities by grouping all near-facility data for a variety of facilities (manufacturing, processing, e-waste, disposal) to estimate a generic "near-facility" exposure. By estimating exposure in this manner, EPA could take advantage of the larger number of monitoring studies or modeled estimates.

However, EPA intends to further assess how comparable locations around

incineration sites would be to those around manufacturing, processing, e-waste, and other disposal facilities. There are factors that may either increase and decrease emissions and potential concentrations around these facilities. For example, elevated temperatures are likely to eliminate some amount of possible TBBPA and its combustion products which could reduce overall exposures. The waste stream and content of TBBPA in materials as part of this waste stream are likely to be highly variable and could result in emissions that are higher or lower than those in manufacturing and processing facilities. Comparison of facility specific information could inform which categories of incineration may be sufficiently different from manufacturing and processing facilities to potentially warrant environmental sampling.

Therefore, to complement the existing data, EPA could collect available information related to estimating potential extent and magnitude of exposure (for example, the number and location of incineration facilities in the U.S. and the types and volumes of products that are accepted by these sites). Waste disposal by incineration as used in the United States could be then compared with the processes used in the studies assessing the foreign facilities. However, the petition does not address this possibility, let alone explain why a testing order under section 4 would be necessary on this point. If the processes are similar, EPA could extrapolate from foreign facilities to U.S. facilities. If EPA determines these previously indicated approaches are not reasonable to determine exposures, then sampling of soils, sediments and waters in the vicinity of facilities and air to which workers may be exposed at facilities known to incinerate TBBPA or TBBPA-containing products, as requested by the petitioners, may be necessary, but could be more strategic and better targeted when based on deliberate evaluation of available existing data and information.

6. *Exposure to degradation by-products.* *a. Degradation in water or soil.* The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict degradation of TBBPA in water by direct photolysis. Studies identifying photodegradation products of TBBPA formed by direct photolysis in water under laboratory conditions (Ref. 92) were identified after the Problem Formulation and Initial Assessment document was published. Therefore, the photodegradation in water test (OCSPP

Test Guideline 835.2240) (Ref. 93), requested by the petitioners, is not needed.

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict reactions resulting from chemical or electronic excitation transfer from light-absorbing humic species rather than from direct sunlight for TBBPA. A study identifying indirect photodegradation products of TBBPA formed by indirect photolysis in water under laboratory conditions (Ref. 94) was identified after the Problem Formulation and Initial Assessment document was published. Therefore, the indirect photolysis in water test (OCSPP 835.5270) (Ref. 95), requested by the petitioners, is not needed.

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict degradation of TBBPA in soil by photolysis. Photolysis of TBBPA deposited on soil or applied to soil with sludge is a possible fate pathway, which could involve different pathways and mechanisms other than photolysis in water. Existing aqueous photolysis studies and/or predictive models can be used to reasonably predict the degradation products of TBBPA. Environmental transport and exposure modeling could be conducted using available measured or estimated physical-chemical properties to estimate exposure of degradation products. This approach has been used by others (Ref. 96) to estimate PBT properties for degradation products. Therefore, the photodegradation in soil test (OCSPP Test Guideline 835.2410) (Ref. 97), requested by the petitioners, is not needed.

b. Microbial degradation. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict microbial degradation of TBBPA in soil in aerobic and anaerobic conditions. EPA has identified existing studies/data describing aerobic and anaerobic biodegradation pathways of TBBPA in both soil samples potentially pre-exposed and not pre-exposed to TBBPA. Some studies are discussed in Appendix C of EPA's Problem Formulation and Initial Assessment document (Refs. 81, 98 and 99). EPA identified two additional studies after publication of the Problem Formulation and Initial Assessment document that also address this endpoint (Refs. 82 and 100). These studies allow EPA to reasonably determine transformation products and

predict relative rates from aerobic and anaerobic microbial degradation in soil. Therefore, the aerobic and anaerobic transformation in soil test (OECD Test Guideline 307) (Ref. 101) and terrestrial soil-core microcosm test (OCSPP Test Guideline 850.4900) (Ref. 102), requested by the petitioner, are not needed.

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict aerobic aquatic biodegradation of TBBPA. Studies are available (Refs. 103 and 104) to reasonably determine aerobic aquatic biodegradation pathways and products as discussed in Appendix C of EPA's Problem Formulation and Initial Assessment document (Ref. 2). Therefore, the aerobic mineralization in surface water-simulation biodegradation test (OCSPP Test Guideline 835.3190) (Ref. 105), requested by the petitioner, is not needed.

As noted in the exposure from disposal discussion, the petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict degradation processes of TBBPA, which would be episodically and/or continuously released to wastewater. The simulation tests to assess the primary and ultimate biodegradability of chemicals discharged to wastewater (OPPTS Test Guideline 835.3280) (Ref. 80), which the petitioner cited in the discussion about exposure to degradation by-products, is not needed.

c. Combustion products. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict potential combustion products of TBBPA. The reference to combustion testing cited by the petitioners and others is available (Refs. 62 and 106). However, knowledge of the types and volumes of TBBPA-containing products is needed to use this data to estimate potential exposures to combustion products. As stated in the Problem Formulation and Initial Assessment document (Ref. 2; page 91), "... contribution of TBBPA to combustion byproducts is not possible to determine." However, EPA could acquire this information from recycling and incineration facilities using approaches described in Units IV.C.4. and IV.C.5.b. The petition does not address this possibility, let alone explain why a testing order under section 4 would be necessary on this point.

d. Toxicity of degradation products. The petition does not set forth facts

demonstrating that there is insufficient information available to EPA to reasonably determine or predict characterization of TBBPA degradation products, and, as stated in Units IV.C.5.a, IV.C.6.a, and IV.C.6.b., EPA has an understanding of the products potentially formed from TBBPA degradation (*e.g.*, tri-, di-, and monobromobisphenol A, bisphenol A, TBBPA—bis(methyl ether), isopropyl dibromophenols). EPA can use predictive models (*e.g.*, EPA's EPISuite models (Ref. 107) to estimate the key physical-chemical properties of these degradants. EPISuite models have been validated and peer reviewed, and TBBPA degradates are chemicals for which EPISuite models are suitable for estimating (*i.e.*, are within applicability domains of EPISuite models). EPISuite has been used for estimating chemical properties in risk assessments conducted by the USEPA, the EU, and Canada. Therefore, the use of the EPA series 830 Group B testing guidelines (Ref. 108), requested by the petitioners, is not needed.

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict toxicity effects of TBBPA degradation products to mammals and birds. The petition did not reflect a comprehensive search and review for existing toxicity data on potential degradation products, and EPA's Problem Formulation and Initial Assessment document (Ref. 2) did not purport to represent such a comprehensive search for degradation products. To address the need for mammal or avian toxicity under EPA's current approach, EPA would conduct a comprehensive literature review to identify existing data for these chemicals or for analogs. Following identification and review of existing data, if EPA deemed specific testing necessary to fill identified data gaps, EPA would consider testing according to EPA series 850 Ecological Effects Test Guidelines (Ref. 109), EPA series 870 Health Effects Test Guidelines (Ref. 110), or appropriate OECD Guidelines.

The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict the toxicity effects of TBBPA degradation products to aquatic organisms. The petition did not reflect a comprehensive search and review for existing toxicity data on potential degradation products, and EPA's Problem Formulation and Initial Assessment document (Ref. 2) did not purport to represent such a comprehensive search. To address the need for aquatic toxicity under EPA's

current approach, EPA would conduct a comprehensive literature review to identify existing data for these chemicals or for analogs. EPA also believes there are alternative approaches available to EPA regarding ecological effects of TBBPA degradation products on aquatic organisms. EPA could use EPA's ECOSAR (Ref. 111) to estimate the aquatic toxicity of these degradants. ECOSAR is an expert system and collection of models (*i.e.*, Quantitative Structure Activity Relationships) that estimate toxicity from structure and physical-chemical properties of a chemical. The models incorporated into ECOSAR have been validated and peer reviewed. ECOSAR models are suitable for estimating toxicity of potential TBBPA degradates (*i.e.*, TBBPA degradation product chemicals are within the applicability domains of ECOSAR models). Therefore, the use of the EPA series 850 testing guidelines (Ref. 109), requested by the petitioners, is not needed for aquatic organisms.

Furthermore, EPA's use of available existing toxicity information and modeling approaches reduces the use of vertebrate animals in the testing of chemical substances in a manner consistent with provisions described in TSCA section 4(h).

7. Hazard endpoints. a. Reproductive toxicity, developmental toxicity and neurotoxicity. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict reproductive, developmental and neurotoxicity of TBBPA. Therefore, the reproductive/developmental toxicity screening test (OECD Test Guideline 421) (Ref. 112), NTP's Modified One-Generation Reproduction Study (Ref. 113) and the complementing Developmental Neurotoxicity Study (OECD Test Guideline 426) (Ref. 114), requested by the petitioners, are not necessary. EPA has identified 15 reproductive/developmental toxicity tests conducted by the oral route of which some include evaluation of neurotoxicity endpoints. The available studies include: A one-generation reproduction toxicity test (Refs. 115 and 9); two 2-generation reproduction tests (Refs. 116 to 118); four prenatal developmental toxicity tests, including a developmental neurotoxicity test (Refs. 119 to 122); and six postnatal developmental toxicity tests, with some that also include a prenatal component (Refs. 123 to 128). All of these studies, except Hass et al. (2003) (Ref. 119) and Kim et al. (2015) (Ref. 126), were described in Appendix G of the published Problem Formulation and Initial Assessment document for TBBPA

(Ref. 2). These studies are either equivalent or superior to the methods used in the reproductive/developmental toxicity screening test (OECD Test Guideline 421) (Ref. 112) and the NTP Modified One-Generation Reproduction Study (Ref. 113).

For developmental neurotoxicity, a study for this endpoint by the oral route is available (Ref. 119), and EPA would consider the results of this study when evaluating risks from TBBPA. Although the study was conducted when the Developmental Neurotoxicity Study OECD Test Guideline 426 (Ref. 114) was a draft guideline, the study is adequate for consideration as part of a weight-of-evidence analysis along with the results of a 2-generation reproduction toxicity study that included a neurotoxicity component (Ref. 121).

Furthermore, EPA conducted an in-depth review of the existing dataset of reproductive and developmental toxicity studies identified, as well as additional animal and human data that evaluated neurotoxicity endpoints (Refs. 131 and 116) following the publication of the Problem Formulation and Initial Assessment document (Ref. 2) and determined that the developmental, reproductive and neurotoxicity endpoints are adequately addressed. Therefore, EPA could use this body of existing data in selecting studies for use in risk evaluation.

Furthermore, EPA's use of available existing toxicity information reduces the use of vertebrate animals in the testing of chemical substances in a manner consistent with provisions described in TSCA section 4(h).

b. Amphibian endocrine system. The petition does not set forth facts demonstrating that there is insufficient information available to EPA to reasonably determine or predict adverse endocrine-related effects from exposure to TBBPA. Therefore, the larval amphibian growth and development assay (LAGDA) (OCSPP Test Guideline 890.2300) (Ref. 132) is not necessary. Data are available that address thyroid effects of TBBPA for both bioactivity and dose response (Refs. 57 and 133 to 139). These data include mixed results in amphibians and more consistent results in mammals indicating that changes in thyroid hormones are associated with developmental effects (specifically neurobehavioral effects). Given the weight-of-evidence, EPA does not believe that the LAGDA would significantly change this conclusion. Furthermore, EPA's use of this available existing toxicity information reduces the use of vertebrate animals in the testing of chemical substances in a manner

consistent with provisions described in TSCA section 4(h).

8. *EPA's conclusions.* EPA denied the request to issue an order under TSCA section 4 because the TSCA section 21 petition does not set forth sufficient facts for EPA to find that the information currently available to the Agency, including existing studies (identified prior to or after publication of EPA's Problem Formulation and Initial Assessment) on TBBPA and analogs, as well as alternate approaches for risk evaluation, is insufficient to permit a reasoned determination or prediction of the health or environmental effects of TBBPA at issue in the petition nor that the specific testing the petition identified is necessary to develop additional information, as elaborated throughout Unit IV of this notice.

Furthermore, to the extent the petitioners request vertebrate testing, EPA emphasizes that future petitions should discuss why such testing is appropriate, considering the reduction of testing on vertebrates encouraged by section 4(h) of TSCA, as amended.

V. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

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List of Subjects in 40 CFR Chapter I

Environmental protection, Flame retardants, Hazardous substances, tetrabromobisphenol A.

Dated: March 10, 2017.

Wendy Cleland-Hamnett,

Acting Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

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DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

50 CFR Part 217

[Docket No. 161216999–7232–01]

RIN 0648–BG50

Taking and Importing Marine Mammals; Taking Marine Mammals Incidental to Commercial Fireworks Displays at Monterey Bay National Marine Sanctuary

AGENCY: National Marine Fisheries Service (NMFS), National Oceanic and Atmospheric Administration (NOAA), Commerce.

ACTION: Proposed rule; request for comments.

SUMMARY: NMFS has received a request from the Monterey Bay National Marine Sanctuary (MBNMS or Sanctuary) for authorization to take marine mammals incidental to commercial fireworks displays permitted by the Sanctuary in California, over the course of five years (2017–2022). As required by the Marine Mammal Protection Act (MMPA), NMFS is proposing regulations to govern that take, and requests comments on the proposed regulations.

DATES: Comments and information must be received no later than April 17, 2017.

ADDRESSES: You may submit comments on this document, identified by NOAA–NMFS–2017–0017, by any of the following methods:

- *Electronic submission:* Submit all electronic public comments via the federal e-Rulemaking Portal. Go to www.regulations.gov/#!/docketDetail;D=NOAA-NMFS-2017-0017, click the “Comment Now!” icon, complete the required fields, and enter or attach your comments.

- *Mail:* Submit written comments to Jolie Harrison, Chief, Permits and Conservation Division, Office of Protected Resources, National Marine Fisheries Service, 1315 East West Highway, Silver Spring, MD 20910.

Instructions: Comments sent by any other method, to any other address or individual, or received after the end of the comment period, may not be considered by NMFS. All comments received are a part of the public record and will generally be posted for public viewing on www.regulations.gov without change. All personal identifying information (e.g., name, address), confidential business information, or otherwise sensitive information submitted voluntarily by the sender will be publicly accessible. NMFS will