EPA Response to Public Comments Related to the Supplemental Files Supporting the TSCA Scope Documents for the First Ten Risk Evaluations

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, DC

This document provides the responses of the U.S. Environmental Protection Agency (EPA)/Office of Pollution Prevention and Toxics (OPPT) to the public comments on the supplemental files supporting the scope documents for the risk evaluations of the first ten chemicals that EPA is conducting under the amended Toxic Substances Control Act (TSCA). These supplemental documents discussed the initial systematic review activities for the TSCA risk evaluations, specifically the data gathering and literature screening strategy.

The *Strategy for Conducting Literature Searches* describes the initial methods, approaches and procedures that EPA used for identifying, compiling and screening publicly available information to support the development of the TSCA risk evaluations. The *Bibliography* documents for each TSCA scope document provide the bibliographic citations that were identified from the initial literature search and included based on the title and abstract screening.

EPA released the documents to the public on June 22, 2017. EPA opened the dockets on June 19, 2017 to receive information from the public. The public comment period ended on September 19, 2017.

Table 1 lists the chemical substances under evaluation, docket number information and web links where the *Strategy for Conducting Literature Searches* and *Bibliography* documents can be found along with the associated TSCA Scope documents and public comments. Table 2 summarizes the public comments that EPA received for the supplemental files.

Table 1. Docket and Web Link Information for the TSCA Scope Documents and Associated Supplemental Files

Chemical Name	CASRN	Docket Number	Web link to TSCA Scope, Literature Search Strategy and Bibliography Documents
Asbestos	1332-21-4	EPA-HQ-OPPT-2016-0736	Link
1-Bromopropane (1-BP)	106-94-5	EPA-HQ-OPPT-2016-0741	Link
Carbon Tetrachloride (CCl_4)	56-23-5	EPA-HQ-OPPT-2016-0733	Link
1,4-Dioxane	123-91-1	EPA-HQ-OPPT-2016-0723	Link
Cyclic Aliphatic Bromide Cluster (HBCD)	25637-99-4; 3194-55-6; and 3194-57-8	EPA-HQ-OPPT-2016-0735	Link
Methylene Chloride	75-09-2	EPA-HQ-OPPT-2016-0742	Link
N-Methylpyrolidone (NMP)	872-50-4	EPA-HQ-OPPT-2016-0743	Link
Perchloroethylene (PERC)	127-18-4	EPA-HQ-OPPT-2016-0732	Link
Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone; PV29)	81-33-4	EPA-HQ-OPPT-2016-0725	Link
Trichloroethylene (TCE)	79-01-6	EPA-HQ-OPPT-2016-0737	Link

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	**Commenter**	**Comment Summary**	**EPA's Response**
1	Green Barn Research	EPA should consider other tools for systematic review: EPA has also proposed to extract data results in the DRAGON software. We strongly encourage EPA to also consider other potential software tools that have been developed and actively incorporated into the process of systematic review, such as Swift Reviewer, Active Screener, HAWC (Health Assessment Workplace Collaborative).	*Response for comments #1-3* EPA/OPPT is considering the use of various tools and/or approaches to support the various stages of the systematic review process of TSCA risk evaluations. DRAGON and DistillerSR are examples of tools that EPA/OPPT uses for the systematic review of TSCA risk evaluations. EPA/OPPT is considering the adoption of the OECD Harmonized Templates (OHTs) for extracting various data streams. EPA/OPPT is exploring to use DistillerSR as the tool for data extraction. EPA/OPPT will rely on HERO as the "warehouse" for all citations included in the TSCA risk evaluations. Each chemical assessment has a "project page" that will be made public when EPA publishes the draft risk evaluations. EPA/OPPT is committed to transparency and will provide documentation of how the systematic review has been conducted to support the TSCA risk evaluations.
2	Green Barn Research	EPA should incorporate appropriate tools for updating and evaluating systematic reviews in their chemical assessments. EPA should evaluate the Cochrane Collaboration panel's tool for updating guidance for systematic reviews, published guidance in 2016 for determining when it is appropriate to update a systematic review and outlining the steps for performing the update to assess the applicability of environmental chemicals given that Cochrane systematic reviews. It will be critical for EPA to develop tools to assist with the process of evaluating existing systematic reviews, particularly as this field continues to rapidly expand and more systematic reviews relevant to environmental health questions are published in the scientific literature, potentially of variable quality. One tool which might be helpful for evaluating the risk of bias in systematic reviews is the ROBIS tool, which the NAS committee utilized in their report. Another tool which may be helpful in this process is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), used by authors of systematic reviews to improve the reporting of elements	

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		relevant to the systematic review and meta-analyses. We also strongly recommend EPA identify tools that may potentially not be appropriate for human health chemical assessments without modification, such as those developed in other fields, such as clinical or preclinical animal or human studies.	
3	U.S. Department of Defense	TCE Section 5.3.1, p.15: While EPA has limited its data to that which is publically available, it appears that the software being used by those who will screen the data is proprietary, i.e., IFC's DRAGON. It is not clear whether the public will be able to access this database and/or see how the software instructs, encourages, or limits the options for the reviewer. We suggest that EPA provide snap-shots of pages used by the reviewers, as well as the results of the analyses.	
4	American Chemistry Council/North American Flame Retardant Alliance (ACC/ NAFRA)	We request that EPA provide (1) a clear definition of "off topic" and "on-topic" and (2) a general scope of how "off topic" and "on-topic" studies are anticipated to be utilized in the evaluation. For example, are "off topic" studies only identified and utilized as supporting information to confirm [or reject] information found in "on-topic" studies?	EPA/OPPT included definitions of on-topic and off-topic references on page 2 of each *Bibliography* document that accompanied each TSCA Scope document. Also the definition was included in section 1.3 of each TSCA Scope document. The definitions have also been included in section 3.2.2.1.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations*.

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5	Green Barn Research	EPA should provide exclusion reasons for off topic citations.	*Response for comments #5-6* The *Strategy for Conducting Literature Searches* documents provided the inclusion and exclusion criteria used for the title/abstract screening. References that did not meet the inclusion criteria were excluded and considered *off-topic*. The inclusion and exclusion criteria for full text screening are included in each of the TSCA Problem Formulation documents for the first ten chemical assessments.
6	Green Barn Research	EPA should stratify its exclusion criteria separately at the title and abstract and full text screening steps.	
7	Green Barn Research	EPA should not exclude studies based on language.	EPA/OPPT will translate studies on a case-by - case basis.
8	Green Barn Research	EPA should have two independent reviewers for screening steps.	*Response for comments #8-11* EPA/OPPT pilots the screening criteria to ensure a level of proficiency of each screener in each subject matter area. Additionally, each article is generally screened by two different reviewers. All of the screening decisions are being documented. Refer to the *Strategy for Conducting Literature Searches* documents and section 3.2.2.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations* for more information on the title/abstract screening.
9	Green Barn Research	EPA should clearly document decisions related to the identification and search. Particularly, the number of studies that are reviewed by a senior-level technician and the feedback and guidance provided to individual screeners.	
10	Green Barn Research	EPA should clarify how it will handle discrepancies in the inclusion/exclusion and tagging process and use a third party reviewer as an arbiter for decisions when consensus is not reached.	
11	Green Barn Research	EPA should clearly outline the process for handling anticipated overlap with literature relevant to multiple topics. EPA should describe whether the same reviewer will be responsible for screening papers with inclusion/exclusion criteria across multiple topics or whether different reviewers are responsible only for screening studies for one particular topic.	

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12	Green Barn Research	EPA should explicitly include 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.	The body of information compiled in the *Bibliography* documents for each TSCA scope document will be the primary pool of studies that will be considered in the TSCA risk evaluations along with information submitted during public comment periods prior to the publication of the draft TSCA risk evaluations. Targeted supplemental searches may be conducted to address specific needs for the analysis phase (e.g., to located specific data for building exposure scenarios and modeling).
13	Green Barn Research	EPA should ensure gray literature search results are adequately screened. EPA's gray literature search strategy proposes to utilize Google's API to develop custom searches and return the first 100 results, sorted by predicted relevancy so that the results likely to be most relevant are screened first. We recommend that EPA ensure that an adequate number of search results are screened. EPA should consider "snowball searching," where the citations of included (i.e., on-topic) references are searched as well as using databases such as Web of Science to search for references that cite the included citations.	EPA/OPPT will include backward searching (also called snowball searching) in future searches. EPA/OPPT may refine the search strategy for future assessments to ensure that relevant gray literature is captured.

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14	U.S. Department of Defense	TCE Section 4.4, p.14: With regard to the exclusion criterion, "Links that were broken at the time of the search", an additional search step may find them before exclusion. We suggest that a search engine such as Google be used to see if title of the document is sufficient to obtain a working URL.	Two types of broken links were identified when searching for gray literature: (1) those associated with entire sites that were "down" or inactive and (2) links on active sites that were no longer appropriate. In the event of the latter, particularly for links on EPA's website, which has recently undergone a large-scale reorganization, the title of documents will be searched via Google to determine if the document is available at another location.
15	U.S. Department of Defense	TCE Section 4.4, p.14: In the exclusion criterion for peer-reviewed articles, "peer reviewed literature was assumed to be captured in searches of the databases of peer-reviewed literature." If the databases of peer-reviewed literature are based on journals, books, and government reports, the conclusion in the criterion may not be valid. For TCE for example, Toxicology Excellence for Risk Assessment (TERA, now part of the University of Cincinnati) had an externally peer reviewed analysis of EPA's RfC that was publically available months before it was published in a journal. This may also be true for many analyses and reviews performed in State regulatory agencies that, unlike academia, do not include journal publications in their criteria for professional advancement.	Peer reviewed literature that was captured during the search of the gray literature was excluded only if it was clearly shown to be available in the peer-reviewed literature, for example, with a journal citation and/or DOI. The peer reviewed analysis by TERA referenced in the comment would not be excluded from the results of the gray literature search. The TERA reference will be added to the on-topic pool of references supporting the TSCA risk evaluation for trichloroethylene.

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16	Green Barn Research	EPA should rely on existing IRIS assessments for hazard identification. Moving forward, EPA should complete hazard identification or add additional studies only through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report. For the scoping document, EPA should include all hazards identified in the literature, and not make decisions about their relevance to the risk evaluation until a systematic review has been completed. EPA should develop criteria to evaluate the internal validity (risk of bias) of individual studies, utilizing existing tools that have been developed and empirically demonstrated on environmental health studies such as the Navigation Guide or the Office of Health Assessment and Translation (OHAT approach). We also recommend that EPA not using a scoring system to evaluate study quality. 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 data can be used to support conclusions, but hazard classification should never be made based on high-throughput or other kinds of mechanistic data alone.	*Response for comments #16-18* EPA/OPPT will use previous assessments such as the IRIS assessments as a starting point for identifying key and supporting studies to inform the human health hazard assessment, including dose-response analysis. The relevant studies will be evaluated using the data/information quality criteria in the document entitled *Application of Systematic Review in TSCA Risk Evaluations*. Refer to each of the TSCA Problem Formulation documents for details on how the PECOs are considering the information of the IRIS assessments for setting inclusion criteria for the full text screening. Regarding negative studies, the 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.

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17	National Resources Defense Council (NRDC)	Use of existing IRIS assessments: To assist the Agency in meetings its deadlines for risk evaluations, previous findings on hazard and risk from the IRIS assessments should be presumed valid and incorporated in risk evaluations. Moving forward, EPA should complete hazard identification or add additional studies through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report on Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Disrupting Chemicals (National Academy of Sciences, 2017).	
18	U.S. Department of Defense	TCE Section 3.3.1, p.9-10: The intent appears to be to use the IRIS 2011 evaluation without independent review of the literature, and to start the literature search at January 2010. However, U.S. EPA (2011b) discounts the negative rat studies as "not entirely adequate", even including the NTP 1988 study which was designed to overcome the high mortality in the NCI 1976 and NTP 1990 rat studies that had high mortality (using the same rat strain) by using five different strains of rat. While one was the same as the two previous, presumably as a control, that was not the case for all of the rat strains. Similarly, U.S. EPA (2011b) states "Weaknesses in the evidence include lack of a clear dose-related response in the incidence of cardiac defects, and the broad variety of cardiac defects observed, such that they cannot all be grouped easily by type or reported inhalation studies being negative for developmental toxicity, EPA's document uses the positive results in oral studies to calculate	

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		the RfC. We suggest that, at a minimum, TSCA independently review the data in the negative studies discounted by the IRIS document, as well as any recent publication. These example cited in the full comment demonstrate the discounting credible negative results in favor of positive studies regardless of route of exposure. Use of PBPK modeling is not justified for route-of-exposure extrapolation when data exist for that route of exposure.	

Abbreviations in Table 2	
ACC NAFRA=American Chemistry Council North American Flame Retardant Alliance	NTP=National Toxicology Program
API=Application Programming Interface	OHAT=The NTP Office of Health Assessment and Translation
DOD=United States Department of Defense	OECD=Organisation for Economic Co-operation and Development
DOI=Digital Object Identifier	OPPT=The Environmental Protection Agency Office of Pollution Prevention and Toxics
DRAGON=	PBPK=Physiologically-based pharmacokinetic
EPA=Environmental Protection Agency	PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EPA/OPPT=Environmental Protection Agency Office of Pollution Prevention and Toxics	ROBIS=tool for assessing Risk of Bias in systematic reviews
HERO=Health and Environmental Research Online	TERA=Toxicology Excellence for Risk Assessment
IRIS=Integrated Risk Information System	TCE=Trichloroethylene
NAS=National Academy of Sciences	TSCA=Toxic Substances Control Act
NRDC=National Resources Defense Council	