

January 21, 2020

Comments from Academics, Scientists and Clinicians on the Draft Risk Evaluation for N-methylpyrrolidone (NMP)

Submitted online via *Regulations.gov* to docket EPA-HQ-OPPT-2019-0236

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 the draft risk evaluation for NMP, issued under EPA's Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA").¹ NMP is a solvent produced at more than 160 million pounds every year with a variety of consumer, commercial and industrial uses.² NMP has a host of health hazards including reproductive and developmental toxicity which is especially of concern for pregnant women, children, and men and women of reproductive age.³

EPA has released a draft risk evaluation for NMP that re-evaluates uses already assessed. The 2015 final risk assessment⁴ went through the public comment and peer-review process⁵ before being finalized; EPA concluded the 2015 risk assessment found unreasonable risks for paint stripping uses.⁶ In 2017, EPA proposed regulatory options to mitigate risks from NMP but since failed to take action on this hazardous chemical.⁷ The current assessment reiterates the risk findings from 2015 and also finds additional risks of concern.

By delaying action on a paint stripper ban, the Agency is leaving public health at risk. This is contrary to the mandate under the law, which states that if the Administrator determines a chemical presents an unreasonable risk, the Administrator *shall* promulgate a rule "to the extent necessary so that the chemical substance or mixture no longer presents such risk."⁸ EPA should immediately move forward to finalize a ban on paint stripping uses as proposed in 2017.

In its draft risk evaluation, EPA continues to utilize its TSCA systematic review methodology, which multiple experts criticized for its non-empirically based scoring of studies that may result in downgrading epidemiological studies and leads to excluding relevant studies. Additionally, EPA continues to employ its "hierarchy of preferences" which for this evaluation excludes 39 studies without adequate justification.

¹ US EPA (2019) Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP). Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0017>

² Id.

³ Id.

⁴ US EPA (2015). TSCA Work Plan Chemical Risk Assessment N-methylpyrrolidone: Paint Stripping Use. CASRN 872-50-4. Office of Chemical Safety and Pollution Prevention.

⁵ 78 FR 1856

⁶ 82 FR 7464

⁷ Id.

⁸ 15 USC §2605(a)

EPA finds NMP presents risks of concern for some conditions of use. In reality, these risks are of greater magnitude, and additional conditions of use present risks of concern because of critical scientific flaws in EPA's risk assessment approaches that lead to underestimating risk. We have previously commented on these issues, including: unsupported assumptions about worker use of personal protective equipment (PPE); failure to include known exposure pathways such as air and water; failure to aggregate exposures from known pathways; and inadequate adjustment factors applied to account for susceptible/vulnerable populations.^{9,10,11}

EPA's Science Advisory Committee on Chemicals (SACC) also identified these and other scientific problems in EPA's draft risk evaluations that lead to underestimating risk. The SACC provided clear directions for needed improvements, but the NMP draft risk evaluation does not reflect the SACC's recommended changes.^{12,13} EPA should incorporate the SACC recommendations and other scientifically based changes needed to comprehensively assess risks as required by law before finalizing the NMP evaluation.

Our comments address the following main points:

- 1. EPA should immediately move forward with finalizing a ban on NMP paint stripping uses.**
- 2. EPA's TSCA systematic review methodology for identifying and evaluating the evidence continues to have serious scientific flaws; persistent use of a method which is not evidence-based, lacks transparency, and is not peer reviewed is likely to have resulted in a biased evidence base for the NMP draft risk evaluation.**
 - a. EPA continues to use methods that lack transparency to identify "key/ supporting/ influential information," and does not provide the details of the methods for the approach for using the "hierarchy of preferences" to exclude relevant studies.**
- 3. In a recent report, the National Academies of Sciences, Engineering, and Medicine (NASEM) provided critical recommendations needed to improve the U.S. Department of Defense (DOD) systematic review method used to derive an occupational exposure level for the solvent**

⁹ US EPA (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053>

¹⁰ US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059> and <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056>

¹¹ US EPA (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF PRHE) et al. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0069>

¹² US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. 1-BP TSCA SACC Meeting Minutes Final Report. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061>

¹³ US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1, 4 Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD); SACC July 2019 Meeting Minutes and Final Report Docket. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063>

trichloroethylene (TCE). We highlight key recommendations directly relevant to the TSCA systematic review method which EPA should implement.

- a. A validated systematic review method should be used.**
- b. A protocol is needed prior to commencing the systematic review (also required in EPA’s framework rules).**
- c. A validated evidence evaluation method should be used.**
- d. Best practice methods should be used to synthesize and integrate each evidence stream.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these or any of our previous comments on methylene chloride.

Sincerely,

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DETAILED COMMENTS

1. EPA should immediately move forward with finalizing a ban on NMP paint stripping uses.

In 2017, EPA found that NMP consumer and commercial stripping uses posed an unreasonable risk, with Hispanic and foreign-born workers in the construction trades disproportionately at higher risk, and proposed prohibiting all consumer and commercial uses.¹⁴

In its regulatory analysis, EPA found that a labeling approach not appropriate as “EPA reasoned that warning labels and instructions alone could not mitigate the risks as necessary so that NMP no longer

¹⁴ 82 FR 7464

presents an unreasonable risk (either to users in the general population or to users who are women of childbearing age).”¹⁵

EPA also found that a training/ certification program for commercial users was not appropriate as “EPA viewed the costs and challenges involved in regulating distributors and ensuring that only trained and certified commercial users are able to access these paint and coating removal products as a significant limitation for this approach.”¹⁶

Finally, EPA found that feasible alternatives to NMP paint strippers already existed: “For almost every situation in which NMP is used to remove paints or coatings, EPA is aware of a cost effective, economically feasible chemical substitutes or alternative methods.”¹⁷

The science has been clear since 2017 - NMP is dangerous and prohibition of paint stripping uses is needed to remove unreasonable risks and prevent fetal death, low birth weight, and damage to the kidney, liver, and reproductive system. Unless EPA acts to finalize a ban, NMP exposures will continue to put the population at risk of these and other devastating, debilitating and costly diseases.

EPA has already found that NMP poses an unreasonable risk based on its own definition, and it is therefore required by law to address it. Therefore, we strongly urge EPA to finalize as quickly as possible a rule to prohibit NMP paint stripping uses.

2. EPA’s TSCA systematic review methodology for identifying and evaluating the evidence continues to have serious scientific flaws; persistent use of a method which is not evidence-based, lacks transparency, and is not peer reviewed is likely to have resulted in a biased evidence base for the NMP draft risk evaluation.

a. EPA continues to use methods that lack transparency to identify “key/ supporting/ influential information,” and does not provide the details of the methods for the approach for using the “hierarchy of preferences” to exclude relevant studies.

In our previous comments on EPA’s draft risk assessments we outlined critiques regarding EPA’s approach of relying on “key and supporting/ influential information” and we reiterate these critiques for NMP.¹⁸ EPA’s method for evaluating study quality using a non-empirically based scoring system and ‘hierarchy of preferences’ continues to exclude relevant studies, and application of the method in the NMP draft risk evaluation highlights its fundamental problems.

We strongly recommend against utilizing an approach that has not been peer-reviewed, has not been subject to public comment period, does not meet the requirements of EPA’s regulation, and raises serious concerns about bias in the evidence base of these evaluations. These methodological problems are significant enough that EPA’s risk conclusions are highly likely to be biased in the direction of

¹⁵ Id. Pg. 7502

¹⁶ Id. Pg. 7502

¹⁷ 82 FR 7464 pg. 7513

¹⁸ US EPA (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053>

underestimating risk. EPA is not systematically reviewing the studies it relies on in these draft evaluations, and it is inappropriately excluding a significant proportion of the body of evidence.

On page 47 of the draft risk evaluation, EPA states:

“EPA leveraged information presented in previous assessments when identifying relevant key and supporting data and information for developing the NMP draft risk evaluation. This is discussed in the *Strategy for Conducting Literature Searches for NMP: Supplemental Document to the TSCA Scope document* (U.S. EPA, 2017e).”¹⁹

Echoing our previous comments,²⁰ the supplemental documents EPA references do not contain the phrasing “key and supporting information.” EPA identified between 0-35 key sources that were taken forward to data extraction and evaluation for: environmental fate and transport; releases and occupational exposures; general population, consumer and environmental exposures, environmental hazards, and human health.²¹ There has been and continues to be a lack of clarity on how EPA chose and evaluated the key sources. We have previously given comments on the 1,4- dioxane, HBCD, and 1-BP risk evaluations about how EPA has failed to have a consistent protocol despite the risk evaluation rule laying out a clear guidance.^{22,23}

EPA states that it excluded 39 sources based on its hierarchy of preferences for releases and occupational exposures²⁴ – which we have previously critiqued as a new methodology that the Agency introduced in its draft risk evaluations. This new methodology, to reiterate, is not part of the TSCA systematic review method document, nor in the scope or problem formulation documents, and has not been subject to peer-review or public comment and is not in the framework rules.

Finally, EPA presents data that NMP increases cancer incidence in rodent studies, but does not draw any conclusions about the carcinogenicity of NMP nor carry the cancer endpoint forward for quantitative

¹⁹ US EPA (2019) Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP). Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0017>

²⁰ US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059> and <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056>

²¹ US EPA (2019) Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP). Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0017> pp. 48-52

²² US EPA (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053>

²³ US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059> and <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056>

²⁴ US EPA (2019) Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP). Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0017> pg. 49

risk evaluation.²⁵ Application of a valid systematic review method, such as the Navigation Guide²⁶ or the Office of Health Assessment and Translation (OHAT)²⁷ would allow EPA to draw a conclusion about the overall strength of the body of evidence and certainty in a conclusion about NMP and cancer.

3. In a recent report, the National Academies of Sciences, Engineering, and Medicine (NASEM) provided critical recommendations needed to improve the U.S. Department of Defense (DOD) systematic review method used to derive an occupational exposure level for the solvent trichloroethylene (TCE). We highlight key recommendations directly relevant to the TSCA systematic review method which EPA should implement.

The U.S. Army Public Health Center has developed and applied novel methodology utilizing systematic review techniques to derive an occupational exposure level (OEL) for the solvent trichloroethylene (TCE).²⁸ The U.S. Department of Defense (DOD) asked the National Academies of Sciences, Engineering, and Medicine (NASEM) to review the scientific and technical basis of the new proposed DOD approach and provide analysis of the individual components of the report that that may “*lead to improvements in the accuracy of the proposed process.*”²⁹ The committee identified fundamental issues with DOD’s approach, describing the systematic review DOD produced as a “*critically low-quality review, as it lacked a protocol, had inadequate methods to assess risk of bias, and had incomplete descriptions of individual studies.*”³⁰ Therefore, the committee could not endorse DOD’s approach for deriving the OEL.

A number of the concerns raised by NASEM about the DOD method are also relevant to EPA’s TSCA systematic review method. EPA’s Science Advisory Committee on Chemicals (SACC) raised similar concerns in peer review of the TSCA Draft Risk Evaluations of C.I. Pigment Violet 29 (PV29), 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD).^{31,32}

Below, we highlight the concerns raised by the NASEM on the DOD systematic review method, along with the NASEM’s recommendations to improve the process. As EPA works to improve the TSCA method, it should incorporate the NASEM’s recommendations to DOD along with the recommendations it has received from the SACC.

a. A validated systematic review method should be used.

²⁵ Id. pg. 182

²⁶ 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.

²⁷ National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program; 2019.

²⁸ Sussan, T.E., G.J. Leach, T.R. Covington, J.M. Gearhart, and M.S. Johnson. 2019. Trichloroethylene: Occupational Exposure Level for the Department of Defense. January 2019. U.S. Army Public Health Center, Aberdeen Proving Ground, MD.

²⁹ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD’s Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 1. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

³⁰ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD’s Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 3-4. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

³¹ US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Available: <https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604> D=EPA-HQ-OPPT-2018-0604

³² US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1, 4 Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD); SACC July 2019 Meeting Minutes and Final Report Docket. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063>

The NASEM found that the DOD produced a “critically low-quality systematic review” and questioned why the DOD deviated from “Established systematic review methods [that] have set the bar for objectivity, rigor, and transparency.”^{33,34} This deviation from using established methods means that DOD has to “defend a different approach, which is particularly difficult when applied to a chemical with a large and controversial database, such as TCE.”³⁵

The NASEM has highlighted that in the Institute of Medicine (IOM) report ‘Finding What Works in Health Care: Standards for Systematic Review’ it defines a systematic review as “a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies.”³⁶ There are 21 IOM standards that cover the entire systematic review process that if adhered to, result in a “scientifically valid, transparent, and reproducible systematic review.”³⁷ Several of these elements are included in the AMSTAR-2, the appraisal tool NASEM used to rate the DOD’s systematic review process as a “critically low-quality systematic review.”³⁸ This rating was driven by several factors including the lack of a systematic review protocol, inadequate methods to assess risk of bias, and incomplete description of individual studies.³⁹

Further, several of these IOM methodological standards are incorporated into validated systematic review approaches used currently on environmental health topics, such as the Navigation Guide⁴⁰ and the Office of Health Assessment and Translation (OHAT).⁴¹ The World Health Organization (WHO) is currently utilizing the Navigation Guide methodology to assess the global burden of work-related injury and disease.⁴² Further, these methods have been peer-reviewed, validated and have been recommended for use previously by the NASEM.

³³ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 52. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

³⁴ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 2. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

³⁵ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 2. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

³⁶ IOM (Institute of Medicine). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press

³⁷ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 28. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

³⁸ Shea, B.J., B.C. Reeves, and G. Wells. 2017. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 358:j4008.

³⁹ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 52. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁴⁰ 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.

⁴¹ National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program; 2019.

⁴² Mandrioli, D., Schlünssen, V., Ádám, B., Cohen, R. A., Colosio, C., Chen, W., ... Scheepers, P. T. J. (2018, October 1). WHO/ILO work-related burden of disease and injury: Protocol for systematic reviews of occupational exposure to dusts and/or fibres and of the effect of occupational exposure to dusts and/or fibres on pneumoconiosis. *Environment International*, Vol. 119, pp. 174–185. <https://doi.org/10.1016/j.envint.2018.06.005>

NASEM Recommendation: If DOD’s intent is to perform a credible systematic review, the committee suggests following one of the established methods (e.g., Woodruff and Sutton 2014; NTP 2019).⁴³

Similar to DOD, EPA created a novel method under TSCA that deviates significantly from established methods. EPA should follow this recommendation for its TSCA systematic reviews.

b. A protocol is needed prior to commencing the systematic review (also required in EPA’s framework rules).

The use of pre-established protocols minimizes bias in the evidence base by explicitly defining question formulation, the conduct of searches, and study evaluation, *a priori*.⁴⁴ Most importantly, decision-making transparency throughout the systematic review process is fundamental to the integrity of evidence-based evaluations.⁴⁵ EPA’s 2017 framework rules mandate that the agency use “a pre-established protocol” to conduct risk assessments. Further, in its review of the EPA IRIS program’s proposed systematic review methods, the NASEM stated that “Completing the literature search as part of 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.”

The NASEM stated that:

“No mention of a protocol is made in DOD’s draft report (Sussan et al. 2019), and the methods described were insufficient for understanding all of the steps that were performed. This led to a lack of clarity as to whether a particular step was performed but not discussed in DOD’s draft report, whether the step was omitted, what decisions were made before performing the review, and what decisions were made or changed during the course of the review.”⁴⁶

The use of pre-established protocols minimizes bias in the systematic review process by pre-defining “search terms, search strategy, inclusion/exclusion criteria, and procedures for study selection.”^{47,48} The NASEM highlights that the “*The protocol is a critical component to a systematic review because it*

⁴³ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD’s Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 36. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁴⁴ National Research Council. Review of EPA’s Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014.

⁴⁵ Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. Finding What Works in Health Care: Standards for Systematic Reviews J Eden, L Levit, A Berg, S Morton (Eds.), National Academies Press (US) Copyright 2011 by the National Academy of Sciences, Washington (DC) (2011)

⁴⁶ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD’s Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 30. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁴⁷ National Research Council. Review of EPA’s Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014.

⁴⁸ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD’s Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 29. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

minimizes author bias, allows for feedback at the early stages of the review, facilitates reproducibility, replication, and future updates, and increases transparency and scientific rigor.”⁴⁹

Throughout its report, the NASEM highlights how missing this vital step in the systematic review process has critically reduced the transparency of the DOD’s decision making. For example, the NASEM state, *“the eligibility criteria were not explicitly stated and were not pre-specified in a protocol... how DOD determined the subset of older studies and other expert reviews to include in its evaluation was unclear... DOD’s report does not provide a complete set of information to determine the studies that were included in the systematic review... Furthermore, how 56 animal studies were selected for critical evaluation was not described. In contrast, special attention is given to evaluating the evidence on congenital heart defects, with particular emphasis on reasons to exclude a study... The lack of transparency and inconsistency with standard reporting practices limits the ability to determine the appropriateness of the results from this review or to reproduce and/or update it.”⁵⁰*

To address these issues and to enhance transparency and reproducibility, the NASEM recommended that a protocol describing the methods for the systematic review be published and peer-reviewed **prior to commencing** the review . Multiple past reports by the NASEM have also recommended this critical step.^{51,52,53,54}

NASEM Recommendations: Preparation of a systematic review protocol that details the pre-defined methods and criteria, which is peer-reviewed and publicly posted before the review is undertaken. Pre-specifying the criteria that will be used to include or exclude studies. Documentation of how studies from each evidence stream (human, animal, and mechanistic) are identified, assessed, and synthesized.⁵⁵

Similar to DOD, EPA has not published any protocols for TSCA reviews. EPA should follow these recommendations for its TSCA systematic reviews.

⁴⁹ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 29. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁵⁰ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 32. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁵¹ NRC (National Research Council). 2011. Review of the Environmental Protection Agency’s Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press.

⁵² 2014. Review of EPA’s Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press

⁵³ NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: The National Academies Press

⁵⁴ NASEM. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press

⁵⁵ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 36. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

c. **A validated evidence evaluation method should be used.**

“The NASEM found critical flaws in the design of DOD’s study applicability tool, because it combined criteria for evaluating individual study quality with criteria for evaluating a body of evidence (a collection of studies) and had some elements that are inappropriate for evaluating individual study quality.⁵⁶ Most significantly, the quantitative scores are contrary to standard systematic review practices, as numerical scores falsely imply a relationship between scores and effect or association, along with several other critical limitations.”⁵⁷

In its review of the EPA IRIS program’s method for systematic review, the NASEM strongly supported a methodology that did not incorporate quantitative scoring.⁵⁸ The use of weighted quality scores are not able to distinguish between studies with a high and low risk of bias in meta-analyses and lacks both empirical and statistical justification.^{59,60,61} Therefore, it is vital that the primary studies that underpin evidence-based decision are assessed with transparent and accepted methods.⁶²

Additional issues that the NASEM identified with how the evidence was evaluated was that the *“DOD was inconsistent in the degree to which it evaluated different types of evidence identified with the tool.”*⁶³ The tool was only *“designed to score in vivo controlled animals studies”* and therefore **no evaluation of the epidemiological literature was performed**, even though *“the epidemiological studies are used by DOD to determine potential cancer risks at the proposed occupational exposure level.”*⁶⁴ The NASEM reported it was unclear why DOD did not evaluate this line of evidence. Further, *“the tool was applied only to studies of noncancer outcomes in animals”* with no explanation *“provided for why it was not applied to cancer studies in animals.”*⁶⁵ Therefore, NASEM recommended that the DOD *“abandon the use of this study applicability tool in favor of established tools to assess risk of bias of animal and*

⁵⁶ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 3-4. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁵⁷ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 3-4. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁵⁸ National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press; 2014

⁵⁹ Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *Jama*. 1999;282(11):1054-1060

⁶⁰ Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: The Cochrane Collaboration and Wiley-Blackwell; 2008.

⁶¹ Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. *J Clin Epidemiol*. 2006 Dec; 59(12):1249-56.

⁶² A.A. Rooney, G.S. Cooper, G.D. Jahnke, et al. How credible are the study results? Evaluating and applying internal validity tools to literature-based assessments of environmental health hazards *Environ. Int.*, 92-93 (Supplement C) (2016), pp. 617-629

⁶³ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 34. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁶⁴ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 34. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁶⁵ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 34. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

human studies” and use the “approach developed by the National Toxicology Program’s Office of Health Assessment and Translation.”⁶⁶

NASEM Recommendations: Numeric scores are not used to evaluate studies. Assess risk of bias and quality of individual studies and then, separately, determine certainty in the body of evidence.⁶⁷

Similar to DOD, the TSCA method uses a quantitative scoring system for study evaluation. EPA should follow these recommendations for its TSCA systematic reviews.

d. Best practice methods should be used to synthesize and integrate each evidence stream.

“In the DOD assessment, no separate synthesis and determination of certainty of evidence was conducted for animal and human studies. It was not clear how mechanistic evidence was identified or assessed. Furthermore, Figure 2 in the DOD draft report illustrates that the three evidence streams were to be considered but it is not clear from this figure, or accompanying text, how or if evidence integration was conducted in making any conclusions about hazard.”⁶⁸

As previously demonstrated by the NASEM, when completing the hazard identification process, human evidence should be synthesized and a determination made on the certainty of evidence.⁶⁹ However, despite DOD developing a PECO statement that yielded 58 human epidemiologic studies, human epidemiologic studies were excluded from this synthesis because:

“Due to the generally limited quantitative information on exposure assessment from human epidemiologic studies as well as the known and unknown co-exposures typically inherent in human exposure studies, epidemiologic studies were considered, as mentioned below, as alternative lines of evidence in the selection of the PODs.”

The NASEM highlights that this is inconsistent with best practice and not appropriate.^{70 71}

The NASEM also highlighted that:

“DOD assessments could include separate synthesis and determination of certainty of evidence for animal, human, and, when appropriate, mechanistic evidence....then also include methods for

⁶⁶ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 3-4. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁶⁷ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 36. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁶⁸ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 35. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁶⁹ NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: The National Academies Press.

⁷⁰ NRC. 2014. Review of EPA’s Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press

⁷¹ NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: The National Academies Press.

*integrating the evidence streams to reach a final causal determination of hazard. These measures will strengthen DOD's assessment by allowing rigorous assessment and integration of the robust information on TCE."*⁷²

Such approaches have already been successfully used by the NASEM⁷³, International Agency for Research on Cancer (IARC),⁷⁴ OHAT⁷⁵ and the Navigation Guide.⁷⁶ The process consists of an overall rating in the confidence of the body of evidence for each specified outcome, for each evidence stream. The overall rating should then be translated into a conclusion on the level of evidence for a health effect, and then finally into a hazard identification conclusion. Human epidemiological and animal studies, when available, should then be integrated, while mechanistic data should be used to help support the final conclusions. The NASEM highlight that these approaches for evidence integration, including those of the Navigation Guide and OHAT should be considered by DOD to be incorporated in their systematic review process.

Recommendation: Conduct separate evidence synthesis and determinations about the certainty of the evidence for each stream of evidence and describe how different streams of evidence are integrated.⁷⁷

Similar to DOD, the TSCA method does not have steps for determining certainty of the evidence for each evidence stream or integrating evidence streams to draw conclusions. EPA should follow the recommendations of the NASEM recommendations for its TSCA systematic reviews.

⁷² National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 56. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.

⁷³ NASEM. (2017). Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: The National Academies Press; 2011

⁷⁴ IARC Monographs on the Evaluation of Carcinogenic Hazards to Humans. Lyon (FR): International Agency for Research on Cancer; 2019 Available from:<https://monographs.iarc.fr/wp-content/uploads/2019/07/Preamble-2019.pdf>

⁷⁵ 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; 2019

⁷⁶ 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

⁷⁷ National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Pp 36. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25610>.