

Report of the NJDEP-Science Advisory Board

Prepared by the Science Advisory Board
Public Health Standing Committee

Review of the Division of Science, Research and Environmental Health Draft Guidance for the Development of Human Health Risk Assessment Documents

Approved by the
NJDEP Science Advisory Board

Dr. Judith Weis, Ph.D. (Chair)
Clinton J. Andrews, Ph.D., P.E.
Carolyn Bentivegna, Ph.D.
Anthony J. Broccoli, Ph.D.
John E. Dyksen, M.S., P.E.
Raymond A. Ferrara, Ph.D.
John T. Gannon, Ph.D.
Richard H. Kropp, M.S., P.E.
Robert J. Laumbach, M.D., MPH
Peter B. Lederman, Ph.D., P.E.
Robert J. Lippencott, Ph.D.
Tavit Najarian, Ph.D.
Mark G. Robson, Ph.D.
Nancy C. Rothman, Ph.D.
David A. Vaccari, Ph.D., P.E.
Lily Young, Ph.D.

March 2, 2017

The following report has been issued by the Science Advisory Board to the Commissioner of the
New Jersey Department of Environmental Protection

Response to the Charge Questions regarding:

**Review of the Division of Science, Research and Environmental Health Draft Guidance for the
Development of Human Health Risk Assessment Documents**

This report was initially prepared by the Public Health Standing Committee and sent to the Science
Advisory Board for review. The Science Advisory Board based this final report on those
recommendations from the Public Health Standing Committee.

Members of the Public Health Standing Committee include:

Mark Robson, Ph.D., M.P.H., Chairperson
Elaine Z. Francis, Ph.D.
Michael Greenberg, Ph.D.
Gerald Kennedy, M.S.
Howard Kipen, M.D., M.P.H.
Judith Klotz, Dr.P.H.
Steven Marcus, M.D.
Clifford Weisel, Ph.D.

Science Advisory Board - Public Health Standing Committee

SUMMARY

Human health risk assessment (HHRA) is the process of collecting and assessing information to estimate the probability of adverse health effects in humans who may be exposed to the chemical agent(s) in question. The New Jersey Department of Environmental Protection's (NJDEP) Division of Science, Research and Environmental Health (DSREH) develops HHRA in support of various NJDEP program activities. To assist NJDEP risk assessors in developing a transparent and consistent assessment, DSREH staff has prepared a guidance document for the development and review of NJDEP risk assessments. It should be noted that the title of the document is Risk Assessment but in fact the focus was much more on hazard identification.

NJDEP Science Advisory Board Public Health Standing Committee (PHSC) was asked to review and assist the DSREH in ensuring the guidance document is transparent and consistent for staff scientists developing HHRA documents and to determine whether the guidance document provided clear, reproducible and transparent direction for conducting HHRA while offering flexibility in level of detail and effort. Additionally, the PHSC was asked to evaluate whether the procedures described in the guidance document followed similar approaches of relevant USEPA programs and to evaluate whether the procedures described in the guidance document provided appropriate technical options needed to address chemical-specific issues.

The PHSC members reviewed the guidance document and fifty-two comments were offered by PHSC members. It can be concluded that the guidance document is comparable to relevant USEPA programs but does not appear to be as transparent and as consistent as possible due to ambiguity in assessing bias. The guidance document is limited when offering flexibility in detail and options to address chemical-specific issues due to its lack of evaluation of mechanistic data.

INTRODUCTION AND METHODS

NJDEP Science Advisory Board Public Health Standing Committee (PHSC) was asked to review and assist the DSREH in ensuring the guidance document is transparent and consistent for staff scientists developing Human Health Risk Assessments (HHRA) documents and to determine whether the guidance document provided clear, reproducible and transparent direction for conducting HHRA while offering flexibility in level of detail and effort in order to review the process a guidance document was prepared by three current DSREH toxicologists. They based their document on the previous guidance document that they had prepared for the development of interim criteria risk assessment, HHRA guidance and practices used by regulatory agencies (e.g. USEPA, IRIS, Office of Water, Superfund program) and in accordance with state of the science in HHRA. It provides context and general direction for developing HHRA, as well as options for the peer review of these assessments. The Appendix at the end of this report provides background and contextual information given to the PHSC at the beginning of this project. A peer review was requested of the PHSC. The makeup of the PHSC consisted of nine members who specialized in toxicology, environmental health and risk analysis, occupational medicine and public health. Specifically, the PHSC was asked to focus on two separate yet inter-related activities:

- 1) development of HHRA (e.g. ground water, soil, or air criteria); and
- 2) options for the peer review of these assessments.

Charge questions were to be addressed for both activities. However, this report focused on just the development of HHRA. That is, the first of the two.

There were four charge questions for the review of the DSREH HHRA guidance document.

- 1) Does the document provide clear, reproducible, and transparent direction for conducting HHRA that are scientifically defensible?
- 2) Do the procedures described in the guidance document completely reflect the current HHRA approaches employed by relevant USEPA programs?
- 3) Do the procedures described in the guidance document provide appropriate flexibility in level of detail and effort, while taking into consideration the different types of assessments requested of the DSREH?
- 4) Do the procedures described in the guidance document provides appropriate technical options needed to address chemical-specific issues?

The PHSC reviewed the guidance document and addressed the charge questions summarized above and listed below. The guidance document was distributed to the PHSC members a week before the first group meeting. The first meeting was held to bring together the committee members and NJDEP-DSREH staff/authors to discuss the project of reviewing the *DSREH's Draft Guidance for the Development and Review of HHRA Documents*. In addition, the charge questions were presented to the Committee. The committee was informed of the many resources available that would help in the review of the document. These included peer-reviewed journal articles, publicly accessible authoritative reports (e.g. by the National Research Council), and webinars.

Charge Questions for the Review of the Division of Science, Research and Environmental Health (DSREH) Human Health Risk Assessment Guidance Document.

1. **Please comment on whether the guidance document provides clear, reproducible, and transparent direction for conducting human health risk assessments that are scientifically defensible.**

The PHSC members critiqued the document for lack of information pertaining to the HHRA process, toxicity value and how it is derived and options for the review process. In a consistent, scientifically rigorous and transparent systematic review (SR), all endpoints would be captured. The reliance of DEP on IRIS values (e.g. reference values) was questioned. However, DSREH staff responded that there are regulatory requirements that direct DEP to utilize IRIS values, when available. This requirement would need to be more clearly articulated in a final document.

The most critical recommendations to the document are as follows: background information on HHRA and the SR process should be incorporated at the beginning of the document (e.g. executive summary), words/terms/phrases throughout the document should be clearly defined in a glossary of terms and the structure of the document should provide for a better flow and understanding of the contents within the document (e.g. incorporate flow chart, insert Table of Contents).

Additional comments included:

Recommendation for re-grouping chemicals for more efficient, less time-consuming risk assessment processes.

Explanation of the potential role of epidemiological meta-analyses and how individual studies are used to derive toxicity value.

Consideration of using additional toxicological endpoints that may not be the most sensitive but which may represent more serious or widespread human health concerns.

Clarification of the use of mechanistic data in deriving toxicity values.

This document focuses on the Hazard Identification portion of a Risk Assessment. Each exposure assessment is site specific and needs to fully identify the exposures to both the general population and sensitive individuals to be combined with the Hazard Identification to conduct an adequate Risk Assessment and eventually develop a Risk Management plan. The exposure assessment should consider multi-chemical exposures and non-chemical stressors to encompass all relevant hazardous identification and a complete Risk Assessment conducted.

The PHSC recommends that the document include recommendations that NJ Risk be used to gather information for the RA (Environmental Impacts, Transport in Air, Persistence, Soil Mobility, Bioaccumulation, Aquatic Toxicity, Carcinogenetic/Mutagenicity, Public Perception) since it's such a powerful tool. Risk Assessments are often static and based on the information available as the assessment is being developed, which may lead to static regulations. With the NJ Risk, once an RA is done, the chemicals of concern should be routinely monitored and if any substantive change occurs in the available data, this should trigger a reevaluation of the RA. In this way, we might be able to move towards the RA process becoming more dynamic leading to more dynamic evaluation of sites.¹

The PHSC recommends confirming that there is exposure to a given environmental medium before conducting an irrelevant hazard assessment.

The DSREH Guidance Document is an excellent document with the one caveat as noted in the last sentence of paragraph one in the summary (above) "It should be noted that the title of the document is Risk Assessment but in fact the focus was much more on hazard identification." Thus, it is recommended that the title should be: "SAB PHSC Risk Assessment Report: Focus on Hazard Identification." It may be helpful to also note in the summary that "Exposure" will be addressed in a follow-up to this report.

Background for Charge Question Two: The USEPA develops human health risk assessments through a number of its programs and Offices. Such programs and Offices include, but are not limited to, the Integrated Risk Information System (IRIS) program, Office of Water, and the Superfund program. The Division of Science, Research and Environmental Health generally follows the human health risk assessment approaches of the USEPA since they are the federal agency tasked with environmental protection and due to the prominence of their risk assessments worldwide. However, there is diversity in some of the approaches (e.g., in terms of format, technical detail) used by the different USEPA programs and Offices in developing human health risk assessments.

2. Please comment on whether the procedures described in the guidance document substantively reflect the current human health risk assessment approaches employed by relevant USEPA programs.

There were requests to add more background information to the guidance document. The perceptions of IRIS and the lack of knowledge about the intricate processes within an HHRA are items to address.

The committee noted the need for scientific/technical edits to the document.

¹ Following the final vote by the full SAB to accept this report, a substantive comment was received by an SAB member. This comment suggested that the reevaluation of risk assessments be accompanied with "some cost/benefit analysis or threshold to avoid unnecessary rehashing of risk review for irrelevant changes".

Some comments included:

Need for more information on interim specific and interim generic criteria.

Need for more information on weight of evidence.

Concern that stakeholders' views of the draft guidance document might be influenced by their current perceptions of IRIS.

Concern that the current PHSC review process could cause delays in issuing regulations and standards. Possibly more detail than necessary in the guidance document regarding technical direction, for which authoritative references that provide this technical detail could be cited instead.

Explicit consideration in the reference doses of vulnerable populations (e.g. age, gender, race, ethnicity, poverty, geographic location, comorbidity, genetic susceptibility because of enzyme polymorphisms, etc.) to the exposure and effects.

As a companion to the US EPA IRIS and other documents for Hazard Identification, the US EPA "Guidelines for Human Exposure Assessment", which are currently being updated (<https://www.epa.gov/osa/guidelines-human-exposure-assessment>) should be considered in preparing the Exposure Assessment portion of the Risk Assessment.

Background for Charge Questions Three and Four. The Division of Science, Research and Environmental Health develops a number of different types of risk assessment documents. In some cases, the USEPA Integrated Risk Information System (IRIS), other programs within USEPA, or another federal, state, or international regulatory or health agency has generated a human health assessment or other risk assessment document for the chemical of interest. In such cases, the Division of Science, Research and Environmental Health may incorporate the relevant USEPA document in whole or in part, and therefore, will not necessarily have to derive a risk assessment from "the ground up." Thus, varying degrees of effort may be required by the Division of Science, Research and Environmental Health when developing risk assessment documents. Additionally, scientific considerations for some chemicals may introduce technical issues that require a departure from the default approaches used by USEPA and the Division of Science, Research and Environmental Health for human health risk assessment.

3. Considering the different types of assessments requested of the Division of Science, Research and Environmental Health, please comment on whether the procedures described in the guidance document provide appropriate flexibility in level of detail and effort.

DSREH's guidance document included many improvements. One included the revision of the default approach for searching for relevant literature and identifying potential health hazards for a given chemical. Second, the proposed protocol provided guidance on how to conduct a comprehensive literature search, document literature search results, and screen relevant and non-relevant literature for identifying health hazards and conducting dose-response analyses. Lastly, the protocol called for the use of standardized evidence tables for the clear, concise, and consistent presentation of data, as opposed to a study-by-study textual summary of data for hazard identification. This approach is used for the human epidemiology and animal toxicology evidence streams but not for the review of mechanistic (e.g. in vitro) data. There are many studies providing mechanistic data but full knowledge of mechanism(s) of action is still not available. Since mechanistic studies may be excluded, empirical evidence is not completely taken into consideration when selecting, assessing and evaluating studies.

4. Please comment on whether the procedures described in the guidance document provide appropriate technical options needed to address chemical-specific issues.

The USEPA's IRIS, the NTP and academia are developing approaches for conducting SR for environmental health purposes. Systematic review aims to increase transparency and objectivity but can be time and resource intensive. Systematic review is used in evidence-based medicine (EBM) for the development of treatment guidelines and comparing healthcare interventions. As recommended by the NRC, SR has recently been applied to assessing the human health risks from environmental chemicals. EBM relies on randomized clinical trials whereas HHRA relies on observational studies in humans, animal experiments and in vitro laboratory studies using cellular or sub-cellular systems and this is one potential option in using SR.

Assessing risk of bias is a critical step in the SR process. Krauth, Woodruff, and Bero (2013) identified a wide variety of instruments developed for assessing risk of bias and other methodological criteria of animal research. However, there is no universally accepted approach to evaluating the methodology and potential biases of animal studies. These studies are important in evaluating potential harm from exposure to environmental chemicals or safety of drugs prior to human testing. In DSREH's guidance document and across other agencies that conduct health assessment (e.g., USEPA), there is no guidance on evaluating the methodology and potential biases of mechanistic studies. The lack of guidance for these important studies can lessen the credibility of a HHRA and hurt the transparency and consistency of this process.

There are many SR protocols listed in PROSPERO and used among various agencies. Moving forward, it would be recommended that an outside agency (i.e., private or governmental) work on developing guidelines for risk assessments to serve all the regulatory agencies, either federal or state. This will ensure the guidelines are consistent, transparent and scientifically up-to-date. The DSREH guidance document was tailored for HHRA related to environmental chemicals associated with air, soil and groundwater. A recommendation would be to develop a guidance document that can be used universally to evaluate human, animal and mechanistic data for all types of environmental chemicals. This hypothetical outside agency would need to be diverse and display expertise and experience in the systematic process. Having trained professionals evaluating a process is critical, the PHSC came from various backgrounds ranging from environmental health to toxicology. However, the PHSC could have been more diverse and included professionals not related to risk assessment or public health.

RESULTS

The PHSC members reviewed DSREH's Draft Guidance for the Development and Review of HHRA Documents. PHSC committee members offered 52 comments. These comments were grouped into the following broad categories: clarification needed (23%), editorial/structural changes (21%), undefined words/phrases (19%), background information needed (15%), scientific/technical changes (15%), strictly comments (4%) and IT requests (2%).

It can be concluded that the guidance document is comparable to relevant USEPA programs but does not appear to be transparent and consistent due to ambiguity in assessing bias. Lastly, the guidance document is limited when offering flexibility in detail and options to address chemical-specific issues due to its lack of evaluation of mechanistic data.

APPENDIX

Review of the Division of Science, Research and Environmental Health Draft Guidance for the Development and Review of Human Health Risk Assessment Documents

The New Jersey Department of Environmental Protection's (NJDEP) Division of Science, Research and Environmental Health (DSREH; formerly the Office of Science) is tasked with developing human health risk assessments in support of various NJDEP program activities. In order to ensure that assessments are developed and peer reviewed using a process and format that is transparent and consistently applied by NJDEP risk assessors, DSREH staff have prepared a draft guidance document for the development and review of NJDEP risk assessments. The Public Health Standing Committee (PHSC) is asked to review this draft guidance document and address the charge questions listed herein.

The PHSC is tasked with the review of a single draft guidance document that provides proposed direction for two separate yet inter-related activities: the first is the development of various types of human health risk assessments (e.g., ground water, soil, or air criteria), and the second is peer review of these assessments. Since these two activities within the draft guidance document can each be considered as stand-alone documents, the PHSC may wish to designate two Workgroups, one to review the protocol for developing human health risk assessments and the other to review the options for peer review of these assessments.

As part of their appraisal of the DSREH draft guidance document, the PHSC may identify differences in how DSREH and other regulatory or health agencies conduct human health risk assessment and peer review. A unique challenge for the PHSC may be recognizing to what extent such differences may result from the resources available to NJDEP versus the resources of other (e.g., federal) agencies that conduct human health risk assessments. Additionally, the PHSC may consider what the implications of these differences may be for the NJDEP human health risk assessments.

In order to address the assigned charge questions, it will additionally be necessary to understand the impetus for and structure of the DSREH guidance document, current human health risk assessment approaches, and structure of the peer review of DSREH human health risk assessments.

Impetus for preparing a guidance document for the development and review of DSREH human health risk assessments

- DSREH recognizes a need for a transparent and consistent protocol that staff scientists can refer to when developing human health risk assessment documents.
- To remain current with the state-of-the-science for human health risk assessment, DSREH wishes to consider and incorporate, to the extent possible, current practices used by regulatory and/or health assessment agencies, in particular the USEPA.
- As no formal external process currently exists, the NJDEP Commissioner requested the development of options for the peer review of DSREH human health risk assessments.

Structure of the guidance document

- The guidance document is structured to provide context and general direction for developing the hazard identification of human health risk assessments and to provide options for conducting subsequent peer review.
- The functional and statutory **context** by which DSREH develops human health risk assessments are provided in the *Preface*, *Purpose*, and *Background* sections.
- **General direction** for developing specific sections of human health risk assessment documents are provided in the *Format and Content of Human Health Risk Assessment Document* and *Human Health Risk Assessment Approaches* sections as well as Appendices 1 through 6.

- **Options** for the peer review of DSREH human health risk assessments are provided in the *Review Process* section and Appendix 7.
- The revised US EPA Guidelines for Human Exposure Assessment under development is providing a source for systematically reviewing measurement and modeling approaches to determine exposures from environmentally contaminated sites and human behavior that result in contact with toxic agents.

Systematic review as an emerging practice in human health risk assessment

- Systematic review is an investigative approach for conducting literature-based reviews that employs pre-determined methods for identifying, selecting, assessing, and summarizing data (IOM, 2011; Rooney 2012; Birnbaum et al., 2013).
- This approach aims to increase transparency and objectivity but can be time and resource intensive.
- While traditionally used in evidence-based medicine (EBM) for the development of treatment guidelines and comparing healthcare interventions, systematic review has recently been applied to assessing the human health risks from environmental chemicals, as recommended by the National Research Council (NRC, 2011; 2014).
- The USEPA's Integrated Risk Information System (IRIS; USEPA, 2013), the National Toxicology Program (Rooney et al. 2014), and academia (i.e., the Navigation Guide; Woodruff et al., 2011) are developing approaches for conducting systematic review for environmental health purposes.
- There are unique challenges for applying systematic review to assessing and predicting the risk from environmental chemicals. Whereas EBM generally relies on randomized clinical trials (RCTs), human health risk assessment relies on observational studies in humans (rarely RCTs), animal experiments, and *in vitro* laboratory (i.e., mechanistic) studies using cellular or sub-cellular systems.

Notable elements of the proposed protocol for developing DSREH human health risk assessments

- In preparing the guidance document, DSREH revised its default approach for searching for relevant literature and identifying potential health hazards for a given chemical. Additional steps for conducting human health risk assessments (e.g., dose-response analyses, criterion derivation) were not updated but still generally follow the standard practices of USEPA.
- The proposed protocol provides guidance to conduct a comprehensive literature search, document literature search results, and screen relevant and non-relevant literature for identifying health hazards and conducting dose-response analyses.
- For hazard identification, the proposed protocol calls for the use of standardized evidence tables for the clear, concise, and consistent presentation of data, as opposed to a study-by-study textual summary of data. Such an approach is proposed for the human epidemiology and animal toxicology evidence streams but not for the review of mechanistic (e.g., *in vitro*) data.

Peer review of DSREH human health risk assessments

- Peer review of DSREH human health risk assessments is proposed to consist of internal peer review, a public input process, and/or external peer review, as appropriate for the specific assessment.
- All draft human health risk assessments will undergo internal peer review by DSREH toxicologists who were not primary authors of the assessment.
- A public input process exists where interested stakeholders can submit additional data and/or relevant information to NJDEP for some human health risk assessments.
- External peer review will be conducted for certain DSREH human health risk assessments by non-NJDEP scientists with relevant subject matter expertise as well as individuals with experience in the development and review of such assessments.

- Three options are proposed as mechanisms for external peer review. These options vary in terms of administrative effort (e.g., by NJDEP or a contracted entity), cost, and time.

References

Birnbaum LS, Thayer KA, Bucher JR, Wolfe MS. 2013. Implementing systematic review at the National Toxicology Program: status and next steps. *Environ Health Perspect.* 121(4):A108-9. PDF available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3620750/pdf/ehp.1306711.pdf>

Institute of Medicine (IOM). 2011. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: The National Academies Press. PDF available at: <http://www.nap.edu/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews>

National Research Council (NRC). 2011. *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. Washington, DC: The National Academies Press. PDF available at: <http://www.nap.edu/catalog/13142/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-formaldehyde>

National Research Council (NRC). 2014. *Review of EPA's Integrated Risk Information System (IRIS) Process*. Washington, DC: The National Academies Press. PDF available at: <http://www.nap.edu/catalog/18764/review-of-epas-integrated-risk-information-system-iris-process>

Rooney 2012. *Background on Draft NTP Approach for Systematic Review and Evidence Integration for Literature-Based Health Assessments*. PDF available at: http://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2012/december/presentations/rooney20121211_508.pdf

Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect.* 122(7):711-8. PDF available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080517/pdf/ehp.1307972.pdf>

US Environmental Protection Agency (USEPA). 2013. Part 1. Status of Implementation of Recommendations. Materials Submitted to the National Research Council, by Integrated Risk Information System Program, U.S. Environmental Protection Agency. PDF available at: http://www2.epa.gov/sites/production/files/2014-06/documents/iris_program_materials_to_nrc_part_1.pdf

Woodruff TJ, Sutton P; Navigation Guide Work Group. 2011. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. *Health Aff (Millwood)*. 30(5):931-7. PDF available at: <http://content.healthaffairs.org/content/30/5/931.full.pdf+html>

U.S. Environmental Protection Agency (USEPA). 2016. "Guidelines for Human Exposure Assessment" Risk Assessment Forum Peer Review Draft, January 7, 2016, PDF Available at: https://www.epa.gov/sites/production/files/2016-02/documents/guidelines_for_human_exposure_assessment_peer_review_draftv2.pdf