Guidance for the Development of Human Health Risk Assessment Documents

Prepared by

Division of Science, Research and Environmental Health

New Jersey Department of Environmental Protection

December 2017

Table of Contents

Appendices

Glossary

Definitions for underlined glossary terms are taken verbatim or are slightly modified from the USEPA's Integrated Risk Information System (IRIS) glossary, which as of May 2017, can be found at:
https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary#formTop

Benchmark dose lower bound (BMDL): A statistical lower confidence limit on the dose or concentration at the benchmark dose (BMD) or benchmark concentration (BMC), respectively.

Benchmark dose modeling: An approach to dose-response modeling that estimates the dose corresponding to a pre-determined level of response based on fitting a model to empirical dose-response data and consideration of the statistical error in the fit of the model to the data.

Grey literature: Literature that is not published in the formal, peer-reviewed scientific literature. Examples include, but are not limited to, conference abstracts, dissertations, reports from various entities, and book chapters.

Hazard assessment: The process of determining whether exposure to an agent can cause an increase in the incidence of adverse health effects (e.g., cancer, birth defect), the description of those effects, and whether the adverse health effect is likely to occur in humans.

Lowest-Observed-Adverse-Effect Level (LOAEL): The lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

Meta-analysis: Statistical method that combines data from similar studies in order to estimate the effects of an exposure on outcome risk. This approach is typically applied to results from randomized clinical trial and epidemiologic studies.

No-Observed-Adverse-Effect Level (NOAEL): The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

Point of departure (POD): The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response.

Reference value: An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another

suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used.

Risk assessment: The evaluation of scientific information on the hazardous properties of environmental agents (hazard characterization), the dose-response relationship (dose-response assessment), and the extent of human exposure to those agents (exposure assessment). The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (risk characterization).

Slope factor: An estimate of the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100. May also be called "potency factor".

Uncertainty factor: One of several, default factors used in operationally deriving the RfD and RfC from experimental data. These factors usually take values of 1, 3, or 10. The factors are intended to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) uncertainty associated with extrapolation when the database is incomplete. The point of departure is divided by the product of the individual factors to yield the RfD or RfC.

Guidance for the Development and Review of Human Health Risk Assessment Documents

Preface

Risk assessment has been defined to contain some or all of the following four individual steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization (NRC, 1983). "Risk assessment" is used in this document as a general term to describe the human health assessments conducted by the New Jersey Department of Environmental Protection's (NJDEP) Division of Science, Research and Environmental Health (DSREH). DSREH assessment documents can either address chemical-specific risk, which is independent of a particular exposure scenario, or be descriptive assessments, which address the risk under a particular exposure scenario (either actual or hypothetical). Except as noted below with respect to the development of specific regulatory standards and guidelines (see *Exposure Assumptions*), this document largely focuses on the DSREH's approach to chemical-specific risk assessments. Such assessments contain information focusing on hazard identification and dose-response assessment. Although chemical-specific assessments are not linked to a site-specific exposure, they form the health-risk portion of exposure-specific risk (i.e., descriptive) assessments conducted by the DSREH and/or other programs within the NJDEP.

Purpose

The purpose of this document is to provide guidance for the development and review of human health risk assessment documents by the NJDEP[1]. This guidance was developed by the DSREH where it is used <u>primarily</u> for interim soil and/or ground water criteria. However, it can be used for other environmental media as well. The guidance is intended to ensure that assessments are developed and reviewed using a transparent process and format that is consistent among NJDEP DSREH toxicologists. Recognizing that the DSREH develops a number of different types of risk assessment documents, this guidance can be modified on a case-by-case basis as appropriate for the purpose and timeframe of the document under development as well as the intent of the risk management action to be taken. When such modifications are made, they will be noted and a justification will be provided. As the state-of-the-science of human health risk assessment continues to evolve, the DSREH will monitor such changes and modify this guidance and its practices as appropriate. Figure 1 provides a graphical representation of the steps typically associated with the human health risk assessment process as conducted by DSREH.

An earlier version of this guidance document was reviewed by the NJDEP Science Advisory Board (SAB). Appropriate comments and recommendations from that SAB review are reflected in this 2017 version of the guidance document.

---

[1] This document is intended to present general guidance and is not intended to be prescriptive. As such, based on the purpose of a given assessment or the nature of issues specific to the chemical being assessed, all or parts of this guidance can be modified as appropriate.
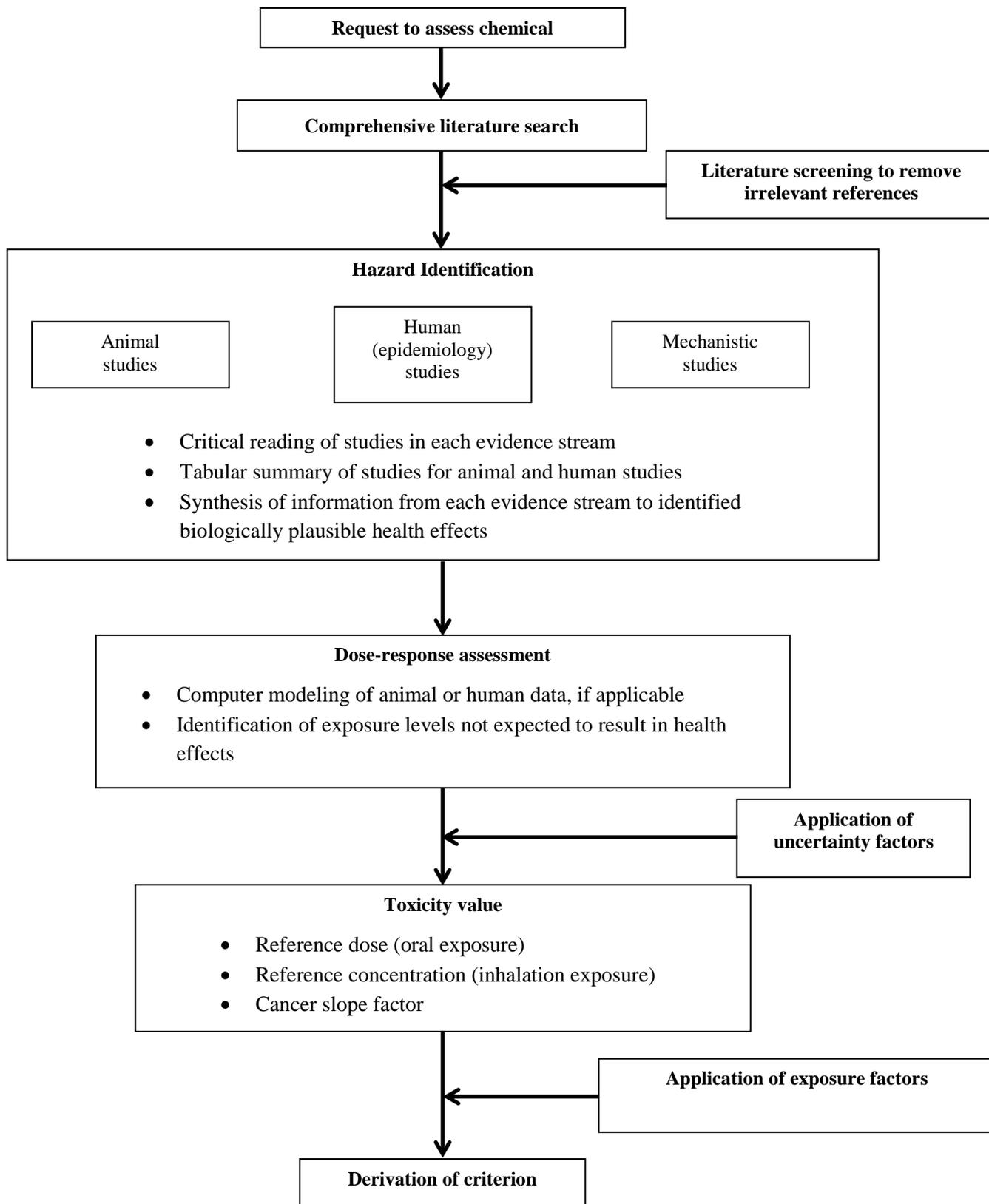
Figure 1. Practical overview of the human health risk assessment process conducted by DSREH.

Background

The New Jersey Ground Water Quality Standards (GWQS; N.J.A.C. 7:9C) provide for the development of interim specific ground water quality criteria for contaminants without promulgated ground water quality criteria. Additionally, if the Department determines that the available health effects (toxicology and epidemiology) information is insufficient to derive an interim specific criterion for a synthetic organic chemical (SOC), the interim generic ground water quality criteria apply. The interim generic criteria are 100 µg/L for chemicals with no evidence of carcinogenicity and 5 µg/L for chemicals with evidence of carcinogenicity (http://www.state.nj.us/dep/wms/bwqsa/gwqs.htm).

The New Jersey Surface Water Quality Standards (SWQS, N.J.A.C. 7:9B-1.4, 1.5, 1.6, 1.14, 1.15) also provide for the development of human health criteria for freshwaters, based on consumption of water and fish, and for saline water, based on consumption of fish (http://www.nj.gov/dep/rules/proposals/091905a.pdf).

Similarly, the New Jersey Soil Remediation Standards provide for the development of interim soil remediation criteria for the direct contact (ingestion and dermal exposure) and inhalation pathways for contaminants without promulgated soil remediation standards. See N.J.A.C. 7:26D of the Soil Remediation Standards at http://www.nj.gov/dep/srp/regs/rs/rs_rule.pdf.

When a request is made to DSREH to conduct a risk assessment for a chemical, NJDEP regulations specify default sources of toxicity factors (e.g., reference dose, cancer slope factor) for ultimately deriving NJDEP standards. The Ground Water Quality Standards (http://www.nj.gov/dep/rules/rules/njac7_9c.pdf) identify the USEPA's Integrated Risk Information System (IRIS) as the default source for toxicity factors. For soil remediation standards, a hierarchy exists where the default source of toxicity factors is the NJ Drinking Water Quality Institute (DWQI) followed by IRIS (http://www.state.nj.us/dep/srp/regs/rs/bb_ingest_dermal.pdf). In some cases, 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 the scenario where there is a pre-existing risk assessment (e.g., in the USEPA IRIS database), the DSREH evaluates the pre-existing risk assessment for scientific rigor as well as for the currency of the scientific literature considered in the assessment from IRIS (or other regulatory or health agency) and accepts or modifies the final qualitative and quantitative (i.e., toxicity value) conclusions as warranted. If no current and scientifically acceptable pre-existing risk assessment exists, the DSREH may generate a risk assessment document using the available primary scientific literature.

Examples of the different types of human health risk assessment documents prepared by the DSREH are listed in Table 1.

Table 1. Types of Human Health Risk Assessment Documents

Document

1. Ground Water Criteria:
    a. Interim
        a) Interim specific (generated from primary scientific literature by DSREH)
        b) Interim specific based on pre-existing value from IRIS or other regulatory agency
        c) Interim generic (if there is insufficient information to develop specific criterion)
    b. Criteria used as basis for promulgated Ground Water Quality Standards

2. Soil Criteria:
    a. Interim
        a) Interim (generated from primary scientific literature by DSREH)
        b) Interim based on pre-existing value from IRIS or other regulatory agency
    b. Criteria used as basis for promulgated Soil Remediation Standards

3. Surface Water Quality Criteria: a) Human health-based ambient water criteria based on IRIS, other regulatory agency, or primary scientific literature
4. Air Criteria based on IRIS, other regulatory agency, or primary scientific literature
5. Drinking Water Health-based Maximum Contaminant Levels (MCLs): Technical Support for NJ Drinking Water Quality Institute (DWQI) Health-based MCL Support Documents. (Note: *The DWQI is an advisory body to NJDEP and uses risk assessment approaches generally consistent with those of the DEP DSREH)*

Format and Content of Human Health Risk Assessment Documents

The general format to be used is attached in Appendix 1. However, additional contaminant-specific topics will be added if relevant to the risk assessment. When appropriate, the focus of the risk assessment (e.g., endpoints to be evaluated in detail) may be informed by previous DSREH evaluation of the chemical. In such cases, justification for focusing the risk assessment based on previous evaluations will be provided.

Human Health Risk Assessment Approaches

As depicted in Figure 1 above, the human health risk assessments developed by DSREH involve a multi-step process. Approaches used by DSREH to develop human health risk assessment approaches are generally consistent with USEPA guidance. Links to current USEPA human health risk assessment guidance documents and the IRIS process for developing human health assessments are found on the USEPA IRIS website at https://www.epa.gov/iris. More concise information about the approaches used by IRIS can be found in the *Preamble to IRIS Toxicological Reviews* that is found at the beginning of the current Toxicological Reviews prepared by IRIS.

Human health risk assessment approaches used by USEPA continue to evolve over time. An example of such an approach is systematic review, which is an investigative approach for

conducting literature-based reviews that employs pre-determined methods for identifying, selecting, assessing, and summarizing data. DSREH monitors and evaluates such changes in USEPA approaches. As appropriate, DSREH will modify its guidance and practices for development of human health risk assessments to remain consistent with new practices (e.g., systematic review) adopted by USEPA.

As currently available, detailed standard operating procedures prepared by the DSREH to date can be found in the Appendices. Guidance is provided for conducting literature searches and screening, and for the preparation of the epidemiology and animal toxicology hazard identification sections. Guidance for preparing other sections (e.g., dose-response analysis) of a DSREH assessment are briefly articulated herein or can be found in the USEPA sources noted above.

Information Sources
A broad and systematic literature search should be performed in order to identify all relevant peer-reviewed and non-peer-reviewed (e.g., grey literature) literature for the chemical of interest. Recognizing that a potentially large number of references with no relevance to the development of the risk assessment document will be identified, a subsequent literature screening process will be performed to identify references that may ultimately inform sections of the risk assessment document (e.g., hazard identification, toxicity value derivation, and human exposure). Documentation of both the literature search and literature screening process will provide transparency to the development of the risk assessment.

A detailed standard operating procedure (SOP) for the literature search can be found in Appendix 2. In brief, the literature search for scientific literature on the chemical of interest should be performed using the CAS Number as well as the chemical name and any common synonyms, which may be identified through searching the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). In consultation with the NJDEP Environmental Research Library (ERL) staff, database-specific search term strings and limitations (e.g., publication dates) should be developed to conduct the literature search.

The two default databases to identify relevant literature are PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Toxline (http://toxnet.nlm.nih.gov/). Additional databases and websites of other state, federal, and international regulatory or authoritative health entities should be searched for references (e.g., health assessments, bioassay data) that may inform aspects of the risk assessment. A list of suggested additional databases and websites can be found in Appendix 2 and includes the National Library of Medicine's Hazardous Substances Data Bank (HSDB), World Health Organization (WHO), as well as various USEPA databases (e.g., IRIS, Provisional Peer Reviewed Toxicity Values). A further resource that may inform the development of a risk assessment is the NJrisk website (http://www.njrisk.org/wp-login.php), which contains information retrieval and exposure modeling components.

Considering that some assessments may be developed over the course of many months during which additional relevant research may be published, a follow up literature search may be required (e.g., 3 or 4 months after the initial search). In general, literature published after this supplemental search will not be considered in the assessment unless the literature has clear potential to change the value of the criterion; textual justification for including this reference will be provided in the assessment.

After identifying literature, all references are manually screened using a set of criteria for relevance to informing hazard identification, dose-response analyses/toxicity value derivation, and human exposure. References that meet certain exclusion criteria (e.g., chemical of interest used as a chemical reagent in a non-toxicological context) are no longer considered during the preparation of the human health risk assessment document. A detailed SOP for the literature screening process can be found in Appendix 3.

Toxicity Evaluation
Toxicity evaluation is defined herein to be inclusive of hazard identification (e.g., carcinogenicity classification, non-cancer endpoints) and dose-response analyses/toxicity value derivation (e.g., slope factor, reference value). For brevity of explanation herein, the toxicity evaluation for New Jersey health-based standards and guidance are developed using risk assessment approaches and assumptions generally consistent with those used by USEPA.

As generally conducted by the DSREH, hazard identification is divided into three separate evidence streams: epidemiological, animal, and mechanistic (e.g., mode of action information). A goal of hazard identification is to identify the most sensitive (i.e., occurring at the lowest exposure levels) and biologically significant endpoints in humans and/or animals following exposure to a given chemical. In addition, consideration should be given to serious adverse endpoints (e.g., mortality). Such endpoints may generally occur at higher exposure levels. However, further consideration of these endpoints is warranted when their dose-response lies close to the most sensitive endpoints. In such cases, additional uncertainty factors may be necessary to provide sufficient protection against these more serious endpoints.

Methodological information and major results from epidemiological and animal toxicology data are presented in standardized evidence tables. A textual, across-study synthesis summarizes information from a given evidence stream to support the DSREH conclusion about a chemical's association with identified health hazards. While the epidemiology and animal toxicology hazard identification synthesis text can be reported independently in separate sections of the document, DSREH assessment authors can, at their discretion and based on chemical-specific issues, integrate these two evidence streams into a single synthesis text. Current SOPs for epidemiological and animals hazard identification sections can be found in Appendices 4 and 5, respectively.

Regarding the use of epidemiological data, meta-analysis can be a useful tool for determining the nature and magnitude of a specific effect when there are a number of studies with seemingly divergent findings. However, the use of meta-analysis is dependent on a sufficient number of compatible epidemiology studies. Both a sufficient number of and/or sufficiently compatible studies are not always available for a specific chemical. Further, if the available studies for a given endpoint are qualitatively consistent in their findings, and the epidemiological data do not lend themselves to the derivation of a quantitative risk metric (i.e., RfD, RfC, cancer slope factor), a meta-analysis may not be necessary or useful.

The mechanistic hazard identification section (e.g., genotoxicity, *in vitro* studies, *in vivo* studies not assessing apical endpoints) can be presented as a cross-study summary of information that informs the nature and relevance of endpoints identified from epidemiological and animal toxicity studies. This section can be based on conclusions drawn from the epidemiological and

animal toxicology hazard identification sections as to which mode of action considerations are relevant to the conclusions of the risk assessment (e.g., human relevance of animal study results, relevance of observations from high-dose studies to potential effects at lower environmental exposures, choice of linear versus threshold dose response model). Mechanistic data do not, themselves, describe adverse health endpoints that would serve as the primary basis for acceptable exposure limits (e.g., a ground water criterion). If available, the use of pre-existing resources (e.g., assessments from other regulatory or health agencies) may be used to inform the mechanistic hazard identification section, at the discretion of the author(s) of the risk assessment. There can be many different types of study designs (e.g., *in vitro*, *in vivo*, *in silico*) for mechanistic data and standardized approaches (e.g., as used by USEPA) may not exist for assessing and evaluating such designs. Accordingly, the format and approach (e.g., use of evidence or summary tables, grouping by study design) in the mechanistic hazard identification section is at the discretion of the DSREH toxicologist(s) preparing the risk assessment. Although toxicokinetic information can provide information that can augment the other mechanistic information for a chemical, it is summarized in a separate section.

Following the review of the epidemiology, animal toxicology, and mechanistic evidence streams, a weight of evidence approach is taken to make conclusions regarding credible health effects caused by a given chemical. As no formal weight of evidence approach is currently employed by USEPA, DSREH toxicologists should apply professional judgment to the integration of results from those evidence streams for identifying non-cancer and cancer endpoints to potentially use as the basis for developing acceptable exposure levels (e.g., a ground water criterion).

Programs within the USEPA sometimes vary in their risk assessment approaches for chemicals classified as *Suggestive Carcinogens* under the USEPA (2005) Guidelines for Carcinogen Risk Assessment or under the analogous classification, *Possible Human Carcinogen* (Group C) under the older USEPA (1986) Guidelines for Carcinogen Risk Assessment. To ensure consistency in New Jersey health-based criteria, an approach has been developed which is used for all NJDEP risk assessments for this category of contaminants. This approach is described in Appendix 6.

Exposure Assumptions
Interim Ground Water Quality Criteria are intended to be protective for lifetime exposure through ingestion of the ground water. Therefore, exposure assumptions (body weight, daily drinking water ingestion volume, and Relative Source Contribution factor) are consistent with those used for chronic drinking water risk assessments (N.J.A.C. 7:9C). Default exposure assumptions should be modified if appropriate. For example, body weight and drinking water ingestion volume for infants should be used if infants are a sensitive subpopulation (e.g. nitrate/nitrite exposure). Alternative approaches for relating exposure to drinking water concentration should be used where appropriate. For example, an approach based on the relationship between drinking water concentration and human serum level has been used to develop risk assessments for exposure to lead and for perfluorinated chemicals in drinking water. As recommended by USEPA, the default Relative Source Contribution (RSC) factor of 0.2 may be increased to a chemical specific value within the range of 0.2 to 0.8 (the ceiling value) if data on non-water exposures support a chemical-specific RSC.

For Interim Soil Remediation Standards, default exposure assumptions for the ingestion-dermal and inhalation pathways for residential and non-residential exposure scenarios are provided in

Basis and Background documents for the Soil Remediation Standards. The Soil Remediation Standards (N.J.A.C. 7:26D) provide for Alternative Remediation Standards for which alternative exposure assumptions may be used if appropriate. See Ingestion-Dermal Exposure Pathway Soil Remediation Standards Basis and Background at:
http://www.state.nj.us/dep/srp/regs/rs/bb_ingest_dermal.pdf and Inhalation Exposure Pathway Soil Remediation Standards Basis and Background at:
http://www.state.nj.us/dep/srp/regs/rs/bb_inhalation.pdf.

Review Process

The draft risk assessment document will be reviewed by DSREH toxicologists who were not the primary author of the document. In addition, similar to the process followed by USEPA for some of its risk assessment documents, certain documents may be subject to external peer review. External peer review of DSREH human health risk-based criteria and guidance is herein defined as the selection of available and qualified non-DSREH scientists to provide comments on a draft document prior to its finalization and application. Peer reviewer candidates can include scientists with relevant subject matter expertise as well as scientists with experience in the development and review of human health risk assessment documents.

The peer review process is distinct from the public input process. The public input process is the public posting on the DEP website of the draft risk assessment document to provide the opportunity for any interested stakeholder (e.g., non-governmental organization, industry, consulting firm, private citizen, non-NJ government agency, academia) to submit additional data and/or relevant information to the DEP. When appropriate, external peer review is conducted after the draft document has been revised to reflect additional information and/or information received through the public input process. Options for external peer-review are provided elsewhere.

Citations

NRC (National Research Council), 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: National Academy Press.

USEPA, 1986. Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum, Washington, DC.

USEPA, 2005. Guidelines for Carcinogen Risk Assessment, Washington, DC, EPA/630/P-03/001F.

DEFAULT FORMAT FOR INTERIM SPECIFIC AND GENERIC CRITERIA DOCUMENTS

Interim Specific Criterion

NOTES: If the criterion is based on a toxicity factor from IRIS or other authoritative source of risk assessment information without modification or with a small modification such as a change in Uncertainty Factors, a much more succinct document than the one outlined below will be provided. The document will state that DSREH has reviewed the basis of the toxicity factor and agrees with it or concludes that it should be modified (e.g., an additional uncertainty factor should be applied). A concise summary of the basis for the toxicity factor (e.g., carcinogenicity classification, citation for principal study, species, endpoint, dose used as point of departure, and uncertainty factors [e.g., for Reference Doses]) will be included.

Contaminant-specific topics not listed below will also be included if relevant to the risk assessment.

 A. Heading: Title, Author, and Date

 B. Summary

 C. Structure of Literature Search

 D. Results of Literature Screening

 E. Physical and Chemical Properties

 F. Background – Production and Use, Other Guidelines, Regulations, and Standards

 G. Environmental Sources, Fate, and Occurrence

 H. Toxicokinetics (absorption, distribution, metabolism, excretion)

 I. Epidemiological Hazard Identification

 J. Animal Toxicology Hazard Identification

 K. Mechanistic Hazard Identification (mode of action information)
  • e.g., genotoxicity/mutagenicity

 L. Integrative Hazard Identification Summary
  • Weight of evidence summary of epidemiological, animal, and mechanistic information to identify non-cancer hazards, if applicable.
  • Choice of appropriate carcinogenicity descriptor based on weight of evidence, if applicable.

M. Toxicity Value Derivation:

- Choice of most appropriate endpoint, with discussion of any other endpoints considered.
- Choice of most appropriate study for the selected endpoint, with discussion of any other studies considered.
- Development of toxicity factor (slope factor or reference value [e.g., Reference Dose])
  - For risk assessments based on non-carcinogenic or cancer endpoint:
    - Identification of Point of Departure (NOAEL, LOAEL, BMDL) as appropriate (*Note: Benchmark dose modeling of dose response should be carried out unless the available data do not support this approach*).
  - For non-carcinogen risk assessments: Choice of uncertainty factors and derivation of reference value.
  - For carcinogen risk assessments: Derivation of slope factor.
- Discussion of uncertainties and confidence in the derivation.

N. Derivation of criterion
- Exposure assumptions (body weight, daily water or soil ingestion rate, etc.)
  - Defaults are modified if sensitive subpopulation (e.g. infants) is appropriate basis for criterion.
- Relative Source Contribution factor for ground water criteria for non-carcinogens
  - Default value of 0.2 may be modified in range of 0.2-0.8 when supported by data.
- Draft Criterion

O. References

P. Appendices

Interim Generic Criterion

NOTES:
1. *Chemicals falling into this category vary widely as far as the amount of data available. Some may have a very complete database, although the appropriate studies for development of a specific criterion are not available, while others may have very sparse databases. Therefore, as much information as is available under the headings below shall be provided.*
2. *As indicated above for Specific Criteria, sections on contaminant-specific topics should also be included if relevant to the risk assessment.*

A. Heading: Title, Author, and Date

B. Summary – one paragraph

C. Structure of Literature Search

D. Results of Literature Screening

E. Physical and Chemical Properties

F. Background – Production and Use, Other Guidelines, Regulations, and Standards

G. Environmental Sources, Fate, and Occurrence

H. Toxicokinetics (absorption, distribution, metabolism, excretion)

I. Epidemiological Hazard Identification

J. Animal Toxicology Hazard Identification

K. Mechanistic Hazard Identification (mode of action information)
   - e.g., genotoxicity/mutagenicity

L. Integrative Hazard Identification Summary

M. Recommendation of generic criterion (carcinogenic or non-carcinogenic) – to include review of reason that a specific criterion cannot be recommended.

N. References

O. Appendices

APPENDIX 2

STANDARD OPERATING PROCEDURE FOR CONDUCTING A LITERATURE SEARCH

This standard operating procedure (SOP) is meant to serve as default guidance for the identification of relevant literature needed for the development of DSREH human health risk assessments. This SOP provides a standardized and transparent approach through the use of relevant databases and search approaches as well as clear documentation of these searches. Recognizing that the DSREH develops a number of different types of risk assessment documents, deviations from this SOP can occur on a case-by-case basis to suit the breadth and urgency of the document in development, and also based on knowledge of additional potential information sources for the chemical being assessed.

1. Develop search term string for conducting database searches. The search term string can be as simple as: "chemical name" OR "CASRN". However, at the discretion of the DSREH scientist and/or after consultation with the Environmental Research Library (ERL) staff, more complex search terms strings can be developed for each database to be searched and to focus the literature search based on the scope of the risk assessment document.

2. Request the ERL to conduct the database literature search. The two default databases to search are:
   - PubMed (http://www.ncbi.nlm.nih.gov/pubmed/; potential limits: selecting a time frame from which to retrieve references).
   - Toxline (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE; potential limits: "Include PubMed records" = no).

3. Document for Step 2 the date of the search, search term string, any limitations, and the number of hits (i.e., number of citations) returned for each database searched.

4. Determine whether other regulatory or health assessment documents exist by searching the following suggested databases/websites:
   - Google (https://www.google.com/; for searching documents produced by, for example but not limited to, ATSDR, CalEPA, IARC, NTP, OECD, WHO).
   - Hazardous Substances Data Bank (HSDB; https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm; for general information on chemical and physical properties, health effects, and regulations and standards from other states).
   - International Toxicity Estimates for Risk (ITER; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?iter; for information from authoritative groups worldwide).
   - USEPA's ChemView database (http://java.epa.gov/chemview; for documents prepared by the USEPA; as of 4/2014, this database is still being populated so searching additional EPA websites is recommended).
   - USEPA's IRIS database (http://www.epa.gov/iris/).

- USEPA's Office of Pesticides Chemical Search database
  (http://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1).
- USEPA's Office of Water Drinking Water Standards and Health Advisories
  (http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf).
- USEPA's Provisional Peer Reviewed Toxicity Values (PPRTV) assessment library
  (http://hhpprtv.ornl.gov/index.html).

5. Document for Step 4 the date of the search, search term string, any limitations, and the number of hits (i.e., number of citations) returned for each database or website searched.

6. Conduct forward and backward searches as needed, based on the identification of primary studies or review articles that appear to be key citations.

7. Document for Step 6 the approach used (e.g., Google Scholar, manual scan of reference list based on scientific judgment) for any forward or backward search, the date of the search, bibliographic information (i.e., author(s) and year) for the key reference(s) used as the basis for the search, the number of hits (i.e., number of citations) returned for the search, bibliographic information of newly identified citations deemed relevant.

8. Request the ERL to conduct updated database searches on selected databases (e.g., PubMed) on a pre-determined basis (e.g., monthly, quarterly) while the assessment is being drafted. Document the updated searches following the appropriate direction from above. Literature published after this follow up literature search may be included in the assessment if that literature has clear potential to change the value of the criterion. Justification for the inclusion of such literature must be provided in the assessment.

Example language to use in DSREH human health risk assessment documents

Text-based documentation in body of document, to be placed between the "Summary" and "Physical and Chemical Properties" heading

<u>Literature search</u>
An initial search was conducted for primary literature [*insert time frame; e.g., "published through April 2014" or "published between the release of the IRIS assessment in 1998 and April 2014"*] using the following databases: PubMed, Toxline, TSCATS, and [*insert others as needed*]. Periodic updates of this search were subsequently performed. Detailed documentation of the database literature searches can be found in Appendix X (Table A).

Additional literature search strategies, such as forward and backward searches using selected key references, were employed to augment the database searches. Results from these searches can be found in Appendix X (Table B).

Tabular-based documentation in an Appendix (example text in BLUE)

Table A. Summary of database search			
Database or website (date of search)	Search term string	Limitations	Number of hits
PubMed (Through 4/20/14) (5/20/14, monthly update) (6/20/14, monthly update)	"Chemical name" OR "CASRN"	None	Through April 2014: 200 May 2014: 10 June 2014: 15
Toxline (4/21/14)	"Chemical name" OR "CASRN" AND ("endpoint 1" OR "endpoint 2" OR "endpoint 3")	Not PubMed	125
TSCATS (4/21/14)	CASRN	None	10
Google (4/25/14)	Using "Chemical name" searched the following websites for health assessment documents: ATSDR, IARC, NTP, OECD, WHO	None	5
ChemView (4/22/14)	CASRN	None	8
Additional databases as necessary			

Table B. Summary of additional search strategies		
Approach (date of search)	Selected key references to search	Additional references identified (Number of citations found; citations)
Forward search Google Scholar (5/05/14)	Primary study: Smith et al, 2000	3; Lincoln et al, 2002; Wilson et al, 2007; Taft et al, 2013
Backward search Manual search of cited references (5/06/14)	Review study: Adams et al, 2012 Health effects document: USEPA, 2010	2; Duke et al, 1998; Prince et al, 1985 1; King et al, 2008

APPENDIX 3

STANDARD OPERATING PROCEDURE FOR CONDUCTING LITERATURE SCREENING

This standard operating procedure (SOP) is meant to serve as default guidance for the screening of identified literature for relevance, with emphasis on hazard identification, toxicity value derivation, and human exposure, to the development of DSREH human health risk assessments. This SOP provides a standardized and transparent approach through the use of *a priori* and chemical-specific criteria as well as documentation of the screening process. Recognizing that the DSREH develops a number of different types of risk assessment documents, deviations from this SOP can occur on a case-by-case basis to suit the breadth and urgency of the document in development.

1. Screen every reference identified from your literature search (i.e., from database and website searches) to determine potential relevance for identifying health hazards, deriving toxicity values, and understanding human exposures for the chemical in question.

    1.1. The decision of relevance for a given piece of literature can be:
        1.1.1. **Exclude**: deemed not relevant to hazard identification, toxicity value derivation, or human exposure, not required to mention this type of reference in the document; or
        1.1.2. **Further consideration**: any sort of information (e.g., primary or secondary data) that may inform hazard identification, toxicity value derivation, and human exposure; some but not all of these references will actually be used (e.g., discussed) and cited in the risk assessment document.

    1.2. These decisions of relevance are based on general *a priori* and sometimes chemical-specific criteria and rationale (see examples in Tables 1 and 2) and are to be made irrespective of the quality and results of the study. While *a priori* criteria may differ between assessment documents, such criteria should always be overtly stated in each assessment (see #1 under "Example language" heading below).

    1.3. Screening can be performed, at the discretion of the DSREH scientist, based on review of the title, abstract, and/or full text.
        1.3.1. Note: during literature screening, references may be identified which may be excluded due to non-relevance to identifying health hazards, toxicity value derivation, or human exposure but are useful for informing supporting sections of the risk assessment document (e.g., the "Background Information" and "Environmental Sources, Fate, and Occurrence" sections). These "excluded" references and information from other health assessments and technical documents (i.e., identified through the formal literature search) may ultimately be used to inform the appropriate supporting sections in the document.

1.3.2. Note: on occasion, during the later stages of document development, literature not excluded during the literature screening process may need to be excluded (e.g., identified as a duplicate reference) with appropriate documentation.

1.3.3. Note: once a reference has been designated as "Further Consideration", forward/backward searches can then be performed at the discretion of the DSREH scientist; additional relevant references identified from the forward/backward searches can then be designated as "Further Consideration" at the discretion of the DSREH scientist.

2. Document the results of the literature screening process (i.e., Step 1; exclude or further consideration).

   2.1. Create a "Master reference list": this list contains those references from the "Literature search list" (i.e., all of the results of database and website searches from the formal literature search) that were designated as "Further consideration" during literature screening plus any additional references identified from forward/backward searches.

   2.2. The "Reference" section of the risk assessment document: contains those references from the "Master reference list" that were actually cited in the risk assessment document as well as any "excluded" references that were used to inform supporting sections such as the "Background Information" and "Environmental Sources, Fates, and Occurrence" sections.

Example language to use in DSREH human health risk assessment documents

1. *Text-based documentation in body of document, to be placed between the "Summary" and "Physical and Chemical Properties" headings but after the "Literature Search" heading*

Literature Screening

Approximately [*insert number*] references were identified from the aforementioned literature search. These references where manually screened (i.e., by title, abstract and/or full text) for relevance to the areas of hazard identification, toxicity value derivation, or human exposure. References considered relevant to informing these areas were selected for "Further consideration" during the preparation of this document. References were excluded if one or more of these criteria were met: [*insert exclusion criteria used for this assessment*]. Based on this screening, [*insert number of "further consideration" references*] references were ultimately designated for "Further consideration". Some references that were excluded for being irrelevant to hazard identification, toxicity values derivation, or human exposure were used to inform supporting sections of this assessment, such as the "Background Information" and "Environmental Sources, Fate, and Occurrence" sections.

Table 1. Examples of general *a priori* exclusion criteria that may be used during literature screening	
Decision	**Criteria**
Exclude	- Article describes analytical methods (e.g., method development) - Chemical being assessed is used as a reagent - Chemical-specific criteria identified by DSREH scientist - Duplicate (of a study already marked for further consideration) - Non-English language reference - Not enough information available to determine relevancy - Related to policy - Related to remediation/biodegradation/environmental fate - Study assessed a mixture - Study focused on ecological effects - Study was in a non-relevant species - Test agent was other than the chemical undergoing the risk assessment

Table 2. Example rationale that can be used for designating a reference as relevant to hazard identification, toxicity value derivation, or human exposure in an DSREH risk assessment document	
Decision	**Rationale**
Further consideration	- Contains primary literature describing potential human health effects - Contains primary literature describing health effects in animals - Book chapters - Editorials/letters to the editor/other correspondences - Health/risk assessments from other agencies or organizations - Humans case reports - Mechanistic studies (e.g., genotoxicity/mutagenicity, *in vitro*, *in silico*) - Meeting abstract/poster - Meta-analyses - Modeling studies (e.g., physiologically based pharmacokinetic) - Review article - Studies assessing health effects from other routes of administration - Studies describing absorption, distribution, metabolism, excretion - Human exposure and biomonitoring studies that would inform the validation or determination of a relative source contribution factor

APPENDIX 4

STANDARD OPERATING PROCEDURE FOR DEVELOPING THE EPIDEMIOLOGY HAZARD IDENTIFICATION SECTION

Purpose: Devise an organized (i.e., easy to follow) epidemiology section that provides a clear and transparent thought process for reaching a conclusion regarding hazard identification and identifying potential studies for dose-response analyses

Context: At this point in document preparation, a literature search has been performed to identify literature and a literature screening (irrespective of study quality) has been performed to identify those references most relevant to hazard identification and/or toxicity value derivation.

Format (headings) of the epidemiology hazard identification section

A. General introduction
- Provides a high-level overview of the entire epidemiological database used for hazard identification
- Includes information such as study designs identified (e.g., cohort, case-control, cross-sectional), populations exposed (e.g., workers, general population, non-occupationally exposed communities), and endpoints
- Discusses any important general issues associated with the epidemiology of the chemical being assessed
- When relevant, discuss the use of previous evaluations for focusing this risk assessment
- Contains language describing the methodology that DSREH used in developing this section (e.g., criteria for including/excluding studies for detailed consideration, evidence tables for individual studies, endpoint-specific summary tables for each endpoint with sufficient evidence, endpoint-specific text)
- Transitions into endpoint-specific paragraphs
- Note: at the discretion of the risk assessment author(s), individual studies may be assessed and/or ranked (e.g., given a study quality descriptor) using professional judgment and/or objective criteria. If electing to conduct such an assessment of studies, the risk assessment author(s) should provide methodology describing the evaluation process (e.g., listing of study quality criteria).

B. Evidence tables for individual studies
- An evidence table containing information on each individual epidemiology study is presented in an Appendix of the assessment document. As an exception, some studies may be excluded from presentation in an evidence table based on stated criteria.
- Criteria for not presenting an individual study in an evidence table are developed by the risk assessor conducting the assessment. For example, "study is not peer reviewed."

- Studies not included in an evidence table, based on criteria such as those above, may still provide important information on the effects of the chemical and can be discussed in the text in an appropriate level of detail.

- The evidence tables use the general format in the example at the end of this standard operating procedure section, and include important study methodology, results, and other relevant information.

C. Endpoint-specific summary tables and text

- Discusses the database for a given endpoint (e.g., liver toxicity) through the following steps:
    1. An endpoint-specific summary table is developed for each endpoint. Every study for which there is an evidence table needs to be included in the summary table for one or more endpoints as appropriate. An example of this table is shown below.
    2. Textual assessment of the evidence (i.e., an across-study summary) for a given endpoint:
        - This assessment of the evidence is a judgment-based process that aims to explain the available data and how these data come together to identify a health hazard. This assessment may describe aspects of the dataset such as magnitude of effect, consistency between studies, the existence of exposure-response gradients, and any other issues specific to the studies being discussed.
        - Textual discussion of any issues bearing on endpoint ascertainment (e.g., changes in disease classification).
        - Textual discussion of any important endpoint-specific issues, which may include but are not limited to: adversity, relevance, significance of the endpoint.
        - Textual summary statement regarding the association between the endpoint and the chemical being assessed.
- Note: depending on the extent of the database for a given endpoint, the above outlined approach may not be necessary for all endpoints.

D. Integration of the epidemiology hazard identification section
- Provides an overall summary of the epidemiology hazard identification section by listing the health hazards identified.
- Discusses overall conclusions about the epidemiology database and about any cross-endpoint issue.

Format for Epidemiology Hazard Identification Evidence Tables

Reference and Study Design	Exposure Measures	Results	Comment
Study: Study Design: Location: Population: Related Studies:	Exposure Assessment: Population-Level Exposure:	Stat Method: [Note to table author, suggested text under the "Stat Method" includes: "covariates and confounders considered included" followed by the appropriate factors (eg, age, sex, alcohol)"] Outcome: Major Findings:	Major Limitations: Quality of Study: Quality

Format for Epidemiology Hazard Identification Endpoint-Specific Summary Tables (using example data for serum lipids)

Citation	Study Population	Study Details	TC	HDL	Non-HDL	LDL	TG	Comments
Fu et al., 2014	China, random selection of attendees to health check-up clinic	*Study Design:* Cross-sectional *Study Size*: n=133 *Study Population Age:* 0-88 years *Exposure (Median)*: 0.37 ng/mL	↑ [a]			↑ [a]	__ [a]	
Lin et al., 2009	General U.S. Population (NHANES, 99-2000 & 03-2004)	*Study Design:* Cross-sectional *Study Size*: adolescents – n=474 / adults – n=969 *Study Population Age*: 12-20 years; > 20 years *Exposure (Mean):* 0.70 ng/mL; 0.81 ng/mL		↓ [b] / __ [b]			__ [b] / __ [b]	
Lin et al., 2013	Individuals with abnormal urinalysis results from population-based screening program in Taiwan	*Study Design:* Cross-sectional *Study Size*: 664 (246 w/ elevated blood pressure and 398 w/ normal blood pressure) *Study Population Age*: 12-30 years *Exposure (GM)*: range 0.38-25.4, males – 1.19, females – 1.00				__	__ [a]	
Mundt et al., 2007	Occupational, U.S. factory	*Study Design:* Cross-sectional and retrospective cohort *Study Size*: n=592 *Study Population Age*: not stated *Exposure (Median)*: not available	↑-	__		__	__	
Nelson et al., 2010	General U.S. Population (NHANES, 03-2004)	*Study Design:* Cross-sectional *Study Size*: n=416 to n=860 *Study Population Age*: <80 years *Exposure (median):* 1.0 ng/mL	↑	__	↑	__		
Starling et al., 2014	Norway, pregnant women, 03-2004	*Study Design:* Cross-sectional *Study Size*: n=891 *Study Population Age*: not stated *Exposure (Median)*: 0.39 ng/mL	__ [b]	↑ [b]		__ [b]	__ [a,b]	

↑ = statistically significant increased association, ↓ = statistically significant decreased association, ↑- = inconsistent positively associated finding (findings from different models resulted in both statistically and non-statistically significant associations), ↓- = inconsistent negatively associated finding, - = not statistically significant, [statistical significant determined at α=0.05]
TC= total cholesterol, HDL= high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol, TG=triglycerides

APPENDIX 5

**STANDARD OPERATING PROCEDURE FOR DEVELOPING THE ANIMAL
TOXICOLOGY HAZARD IDENTIFICATION SECTION**

Purpose: Devise an organized (i.e., easy to follow) animal toxicology section that provides a
clear and transparent thought process for reaching a conclusion regarding hazard identification
and identifying potential studies for dose-response analyses

Context: At this point in document preparation, a literature search has been performed to
identify literature and a literature screening (irrespective of study quality) has been performed to
identify those references most relevant to hazard identification and/or toxicity value derivation
(e.g., reference values, cancer slope factor)

Format (headings) of the animal toxicology hazard identification section
A.   General introduction
- Provides a high-level overview of the entire animal database used for hazard identification.
- Includes information such as study designs identified (e.g., chronic, subchronic, short-term,
  acute, reproductive/developmental), species (e.g., rodents, non-human primates), and
  endpoints.
- Discusses any important general issues associated with the animal toxicology of the chemical
  being assessed.
- When relevant, discuss the use of previous evaluations for focusing this risk assessment.
- Contains language describing the methodology that DSREH used in developing this section
  (e.g., criteria for including/excluding studies for detailed consideration, evidence tables for
  individual studies, endpoint-specific summary tables for each endpoint with sufficient
  evidence, endpoint-specific text).
- Transitions into endpoint-specific text that summarizes and integrates the information on the
  endpoint.
- Note: at the discretion of the risk assessment author(s), individual studies may be assessed
  and/or ranked (e.g., given a study quality descriptor) using professional judgment and/or
  objective criteria. If electing to conduct such an assessment of studies, the risk assessment
  author(s) should provide methodology describing the evaluation process (e.g., listing of study
  quality criteria).

B. Evidence tables for individual studies
- An evidence table containing information on each individual *in vivo* toxicity study is
  presented in an Appendix of the assessment document. As an exception, some studies may
  be excluded from presentation in an evidence table based on stated criteria.
- Criteria for not presenting an individual study in an evidence table are developed by the risk
  assessor conducting the assessment. Examples of possible criteria for exclusion from
  presentation in an evidence table are: study is not peer reviewed; route of administration not
  relevant; duration of study is not sufficient; or *in vivo* study that assesses only mode of

action-related endpoints (e.g. changes in gene expression) and does not assess apical endpoints (e.g., tumor incidence, clinical chemistry, organ weight, histopathology, offspring weight, developmental landmarks, and others).

- Studies not included in an evidence table, based on criteria such as those above, may still provide important information on the effects and mode of action of the chemical and can be discussed in the text (in Animal Hazard Identification and/or Mechanistic Hazard Identification [Mode of Action] sections) in an appropriate level of detail.

- The evidence tables use the general format in the example at the end of this standard operating procedure section, and include important study methodology, results, and other relevant information.

C. Endpoint-specific summary tables and text

- Discusses the database for a given endpoint (e.g., liver toxicity) through the following steps:
  1. An endpoint-specific summary table is developed for each endpoint. Every study for which there is an evidence table needs to be included in the summary table for one or more endpoints as appropriate. An example of this table is shown below.
  2. Textual assessment of the evidence (i.e., an across-study summary) for that endpoint.
     - This assessment of the evidence is a judgment-based process that aims to explain the available data and how these data come together to identify whether or not the chemical causes adverse effect. This assessment may describe aspects of the dataset such as magnitude of effect, consistency between studies, the existence of exposure-response gradients, and any other issues specific to the studies being discussed.
     - Textual discussion of any important endpoint issues, for example: specificity of endpoint measurement, adversity, human relevance, significance
     - Textual summary statement (i.e., a conclusion) regarding the association between the endpoint and the chemical being assessed
  - Note: depending on the extent of the database for a given endpoint, the above outlined approach may not be necessary for all endpoints

D. Integration of the animal hazard identification section

- Provides an overall summary of the animal hazard identification section by listing the health hazards identified.

- Discusses overall conclusions about the toxicity database and about any cross-endpoint issues, including which effect(s) are the most sensitive endpoints of toxicity based on relative doses at which they occurred.

Format for Animal Toxicology Hazard Identification Evidence Tables

Reference and Study Design	Results	Comment
[Author et al. (YEAR)] **Species and strain:** [insert species, strain] [insert age of animals] **Group size:** [insert n/sex/group] **Test article and vehicle:** [insert test article and vehicle] **Route of exposure:** [insert route of exposure] **Exposure levels:** [insert administered and/or internal dose/concentration, as appropriate] **Exposure regimen:** [insert # day/week for # duration] [insert other critical information, if applicable] **Related studies:** [insert if additional studies are required for the interpretation of methods or results or if this study is an interim report of a longer study]	(table 1 below) (table 2 below) [insert qualitative description of study results as necessary]	**Major Limitations:** **Quality of study:**

[insert endpoint] *percent change compared to control and/or absolute values*

	Exposure level			
	0	1	2	3
Male	---	5%	15%	45%
Female	---	1%	12%	30%

[insert endpoint] *incidence (percent)*

	Exposure level			
	0	1	2	3
Male	---	0/10 (0)	1/10 (10)	5/10 (50)
Female	---	2/10 (20)	4/10 (40)	7/10 (70)

(Treated value – control value) / control value x 100%

Format for Animal Toxicology Hazard Identification Endpoint-Specific Summary Tables (using example data for renal toxicity)

Citation	Species	Dose	Duration	Endpoint	NOAEL*	LOAEL*	Comments
Smith et al. (2010)	Rat	0, 0.019, 0.09, 0.44 mg/kg/day Gavage	13 weeks	↑ kidney weight Histopathological changes in the kidney	*Males:* Administered: 0.44 mg/kg/day Internal (serum): 0.52 ng/ml *(Females not evaluated).*	--------	
Jones et al. (2008)	Rat	0, 0.019, 0.09, 0.44 Gavage	18-21 weeks	↑ kidney weight (absolute and relative)	*Males:* 0.019	0.09	
					Females: 0.125	0.44	
				Renal cell hypertrophy	*Males:* 0.09	0.44	
					Females: 0.44	----------	
* NOAELs are defined herein as the highest dose that did not produce a statistically significant (e.g., p<0.05) effect and LOAELs are defined herein as the lowest doses with statistically significant (e.g., p<0.05) effects. For some endpoints, there were dose-related trends that included non-statistically significant changes at lower doses than the LOAEL.							

APPENDIX 6

RISK ASSESSMENT APPROACH FOR SUGGESTIVE/POSSIBLE HUMAN CARCINOGENS

In 2000, NJDEP adopted a new risk assessment approach for chemicals considered Possible Human Carcinogens (Group C) under the 1986 USEPA Cancer Risk Assessment Guidelines (USEPA, 1986). The category Possible Human Carcinogen (Group C) under the 1986 USEPA guidelines is analogous to the Suggestive Evidence of Carcinogenic Potential descriptor described in the current 2005 USEPA Guidelines for Cancer Risk Assessment (USEPA, 2005). This approach of equating the 1986 Group C descriptor with the 2005 Suggestive descriptor is used consistently throughout NJDEP for the development of health-based standards, criteria, and guidance for drinking water, ground water, surface water, soil, and air, as well as by the New Jersey Drinking Water Quality Institute in recommending Health-based Maximum Contaminant Levels for drinking water (and the terms combined as "Suggestive/Possible Human Carcinogens").

The approach adopted in 2000 is intended to harmonize the approaches for such chemicals that are used by the USEPA Office of Water and the USEPA Superfund program. The earlier NJDEP approach (i.e., before 2000) for these chemicals preferentially used the Reference Dose for non-carcinogenic effects, with incorporation of an additional uncertainty factor of 10 to account for possible carcinogenic effects. If no Reference Dose was available, a risk assessment based on the slope factor at a 10^{-5} risk level was used. This approach was based upon the paradigm used for Group C chemicals by the USEPA Office of Water.

The approach used since 2000 by the Department for Suggestive/Possible Human Carcinogens preferentially utilizes a carcinogenic slope factor at the 10^{-6} risk level, which is specified in the A-280 Amendments to the New Jersey Safe Drinking Water Act (N.J.S.A. 58:12A-1 et seq), the Brownfields and Contaminated Site Remediation Act (N.J.S.A. 58:10B-12), and the Ground Water Quality Standards Regulations (N.J.A.C. 7:9C). If available, a slope factor from USEPA or other valid source that is judged technically sound by the NJDEP may be used.

If such a slope factor is not available, the pre-2000 approach is followed using the Reference Dose with an additional uncertainty factor of 10. An exception is made if the risk assessment based upon the Reference Dose (without an additional uncertainty factor of 10) is more protective than the risk assessment based on the slope factor at the 10^{-6} risk level; in this case, the Reference Dose is used as the basis for the risk assessment.

This revised NJDEP approach integrates the approaches used for Suggestive/Possible Human Carcinogens by the USEPA Office of Water, which has preferentially used the Reference Dose with an additional uncertainty factor of 10 (USEPA, 1985), and the USEPA Superfund program, which has preferentially used the slope factor at a 10^{-6} risk level (USEPA, 1991).

Citations

USEPA, 1985. National Primary Drinking Water Regulations; Synthetic Organic Chemicals, Inorganic Chemicals, and Microorganisms. Fed. Reg. 50 (219): 46936-47025.

USEPA, 1986. Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum, Washington, DC.

USEPA, 1991. Risk Assessment Guidance for Superfund (RAGS) Part B. Available at: http://www.epa.gov/oswer/riskassessment/ragsb/

USEPA, 2005. Guidelines for Carcinogen Risk Assessment, Washington, DC, EPA/630/P-03/001F.