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Office of Chemical
Safety and Pollution Prevention

Guidance to Assist Interested Persons in Developing and Submitting Draft Risk Evaluations Under the Toxic Substances Control Act

June 2017

DISCLAIMER

This Guidance does not constitute rulemaking by the United States Environmental Protection Agency (U.S. EPA), and cannot be relied on to create a substantive or procedural right enforceable by any party in litigation with the United States. As indicated by the use of non-mandatory language such as "may" and "should," it provides recommendations and does not impose any legally binding requirements.

The TSCA statutory provisions and EPA regulations described in this document contain legally binding requirements. This document is not a regulation itself, nor does not it change or substitute for those provisions and regulations. While EPA has made every effort to ensure the accuracy of the discussion in this guidance, the obligations of EPA and the regulated community are determined by statutes, regulations, or other legally binding requirements. In the event of a conflict between the discussion in this document and any statute or regulation, this document would not be controlling.

The guidance is not applicable to risk evaluations developed to support other EPA statutes or programs. Interested persons are free to raise questions and objections about the substance of this guidance and the appropriateness of the application of this guidance to a particular situation. EPA may take action that is at variance with the recommendations in this document and may change them at any time without public notice.

This is a living document and may be revised periodically. EPA welcomes public input on this document at any time.

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This guidance document was developed by the U.S. EPA, Office of Chemical Safety and Pollution Prevention, Office of Pollution Prevention and Toxics.

GLOSSARY OF TERMS AND ABBREVIATIONS

AOP	Adverse Outcome Pathway
CFR	Code of Federal Regulations
EPA	Environmental Protection Agency
IRIS	Integrated Risk Information System
MOA	Mode of action
NRC	National Research Council
OECD	Organization for Economic Cooperation and Development
OPPT	Office of Pollution Prevention and Toxics
TSCA	Toxic Substances Control Act
U.S.	United States
U.S.C	United States Code

1 PURPOSE OF THIS GUIDANCE

On June 22, 2016, the "*Frank R. Lautenberg Chemical Safety for the 21st Century Act*" was signed into law, thereby amending the 1976 Toxics Substances Control Act. The amended Toxic Substances Control Act is referred to as *TSCA* hereafter. One of the key features of the amended law is the requirement that EPA prioritize and assess existing chemicals, and manage identified risks. Through a combination of new authorities, a risk-based assessment mandate, deadlines for action, and minimum throughput requirements, TSCA effectively creates a "pipeline" by which EPA will conduct risk evaluation and management of existing chemicals.

The law also requires EPA to develop guidance, which is presented in this document, to assist interested persons (referred as external parties hereafter) in submitting draft risk evaluations which shall be considered by EPA. In accordance with TSCA, the guidance shall, at a minimum, address the quality of the information submitted and the process to be followed in developing draft risk evaluations for consideration by EPA.

This guidance avoids being prescriptive as EPA's approaches – and consequently the guidance that EPA would provide to external parties – will likely evolve over time, and new relevant guidance documents will be developed. EPA's goal is to ensure that external parties have flexibility to use the best available science by adapting and keeping current with changing science. Its contents may be refined, updated, or superseded in the future to capture the latest changes to the risk evaluation process resulting from Agency experience, advances in science, and future guidance which may be developed or updated.

EPA's expectation is that external party draft risk evaluations will be of the same high quality as those developed by EPA. To that end, this guidance discusses the science standards, data quality considerations, and the steps of the risk evaluation process that external parties should follow when developing draft TSCA risk evaluations. Having the key factors and risk evaluation process laid out in this guidance will foster predictability by transparently communicating EPA's expectations.

EPA's vision is to have a sustainable TSCA program that is meaningfully informed by high-quality risk evaluations conducted by external parties. EPA will continue to consider other approaches to ensure that external parties are provided with sufficient information to provide high quality draft risk evaluations to the Agency. For example, EPA may consider the development of a voluntary consensus standard for the conduct of risk evaluations that would be consistent with the requirements in TSCA and would also meet the EPA quality standards

EPA values the opportunity for public involvement to strengthen the guidance document for external party draft risk evaluations. External parties should contact EPA at TSCA-externalparty@epa.gov to discuss any questions about the contents of this guidance document including plans to submit draft risk evaluations for consideration by EPA. Furthermore, the

public can provide comments on the guidance at www.regulations.gov, docket # EPA-HQ-OPPT-2017-0341.

Concomitant with this guidance, EPA is issuing final rules to establish the procedures EPA will use to prioritize chemical substances and conduct risk evaluations for existing chemicals (40 CFR Part 702). External parties are encouraged to read the final rules, including preambles to both rules, to familiarize themselves with the TSCA prioritization and risk evaluation processes. Please visit the EPA website for more information on the TSCA implementation activities.

2 BACKGROUND AND STATUTORY FRAMEWORK

2.1 Statutory Requirements for Risk Evaluations under TSCA

EPA's Office of Pollution Prevention and Toxics (OPPT) is responsible for health and environmental risk evaluations of existing chemicals under TSCA. These risk evaluations are conducted to determine whether a chemical substance or category of chemicals, under the conditions of use, presents an unreasonable risk of injury to health or the environment. The risk evaluations have to be conducted without consideration of costs or other non-risk factors, and must evaluate risks to potentially exposed or susceptible subpopulations that EPA identifies as relevant to the risk evaluation.

TSCA section 6(b) identifies the minimum components EPA must include in all chemical risk evaluations. For each risk evaluation, EPA must publish a document that outlines the scope of the risk evaluation that will be conducted, and that includes the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations the EPA expects to consider. The statute provides that the scope of the risk evaluation must be published no later than six months after the initiation of the risk evaluation. The statute also requires that EPA allow for at least one 30-day public comment period on the draft risk evaluation, prior to publishing a final risk evaluation. Furthermore, there are statutory time limits for completing TSCA risk evaluations. TSCA requires EPA to complete the final risk evaluation within three years from initiation, with a possible six-month extension. External parties are encouraged to go to 40 CFR Part 702 for more information about the procedures for chemical risk evaluations under TSCA.

Each risk evaluation must: (1) "integrate and assess available information on hazards and exposure for the conditions of use of the chemical substance, including information on specific risks of injury to health or the environment and information on potentially exposed or susceptible subpopulations identified as relevant by the Administrator;" (2) "describe whether aggregate or sentinel exposures were considered, and the basis for that consideration;" (3) "not consider costs or other nonrisk factors"; (4) "take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use;" and (5) "describe the weight of scientific evidence for the identified hazards and exposure." When conducting risk evaluations

of metals or metal compounds, EPA must use the March 2007 *Framework for Metals Risk Assessment* of the Office of the Science Advisor (U. S. Environmental Protection Agency, 2007) or a successor document that addresses metals risk assessment and is peer-reviewed by the Science Advisory Board.

Moreover, the statute requires that EPA adhere to specific provisions regarding Scientific Standards and Weight of the Scientific Evidence (herein after referred to as weight of the evidence). Chapter 3 of this guidance document addresses the science standards for draft risk evaluations as articulated in Section 26 (h) and (i) of TSCA [15 U.S.C. 2625(h) and (i)] and 40 CFR Part 702.

Pursuant to TSCA section 26(j) [15 U.S.C. 2625(j)], and subject to TSCA section 14, 40 CFR Part 702 specifies that EPA will provide public access to the following information, as applicable, for a particular risk evaluation: (1) the draft scope, final scope, draft risk evaluation, and final risk evaluation; (2) all notices, determinations, findings, consent agreements, and orders; (3) any information required to be provided to the Agency under 15 U.S.C. 2603; (4) a nontechnical summary of the risk evaluation; (5) a list of the studies, with the results of the studies, considered in carrying out each risk evaluation; (6) the final peer review report, including the response to peer review and public comments received during peer review; and (7) response to public comments received on the draft scope and the draft risk evaluation.

EPA will review this guidance document according to the statutory timeframes set forth in section 26(l)(2) of TSCA, and revise it as EPA determines to be necessary to reflect new scientific developments or understandings.

2.2 Definitions

This section defines key terms that are important to understand when developing a draft risk evaluation. The following definitions are codified in TSCA (15 U.S.C. 2602) or 40 CFR Part 702.33. EPA recommends that external parties consult with the preamble of 40 CFR Part 702 for EPA's interpretation of those definitions that were established in the final rule establishing the procedures for chemical risk evaluations under TSCA.

1. *Aggregate exposure* means the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways.

2. *Best available science* means science that is reliable and unbiased. Use of best available science involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data). Additionally, as stated in

EPA's *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act*, under 40 CFR Part 702.33, EPA will consider as applicable:

- The extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information;
- The extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture;
- The degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented;
- The extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and
- The extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies or models.

3. *Chemical substance* means any organic or inorganic substance of a particular molecular identity, including any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and any element or uncombined radical. Chemical substance does not include
    - any mixture;
    - any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act) when manufactured, processed, or distributed in commerce for use as a pesticide,
    - tobacco or any tobacco product;
    - any source material, special nuclear material, or byproduct material (as such terms are defined in the Atomic Energy Act of 1954 and regulations issued under such Act);
    - any article the sale of which is subject to the tax imposed by section 4181 of the Internal Revenue Code of 1954 (determined without regard to any exemptions from such tax provided by section 4182 or 4221 or any other provision of such Code), and
    - any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device.

4. *Conditions of use* means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of.

5. *Guidance*: any significant written guidance of general applicability prepared by the EPA Administrator.

6. *Pathways* means the mode through which one is exposed to a chemical substance, including but not limited to: food, water, soil, and air.

7. *Potentially exposed or susceptible subpopulation* means a group of individuals within the general population identified by the Agency who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.

8. *Reasonably available information* means information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation. Information that meets the terms of the preceding sentence is reasonably available information whether or not the information is confidential business information, that is protected from public disclosure under TSCA section 14.

9. *Routes* means the particular manner which a chemical substance may contact the body, including absorption via ingestion, inhalation, or dermally (integument).

10. *Sentinel exposure* means the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures.

11. *Uncertainty* means the imperfect knowledge or lack of precise knowledge of the real world either for specific values of interest or in the description of the system.

12. *Variability* means the inherent natural variation, diversity, and heterogeneity across time and/or space or among individuals within a population.

13. *Weight of evidence* means a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.

The terms "*risk assessment*" and "*risk evaluation*" are commonly used interchangeably in the scientific literature and in certain EPA technical guidance documents. *Risk assessment* evaluates available scientific information on the properties of an agent and its effects in biological systems to provide an evaluation of the potential for harm as a consequence of environmental exposure (EPA, 2005).

On the other hand, the term "*risk evaluation*" is used exclusively in this guidance, consistent with the specialized meaning of "*risk evaluation*" under TSCA. "*Risk evaluation*" is the process specified under section 6(b)(4)(A) of determining whether a chemical substance presents an unreasonable risk of injury to health or the environment under the conditions of use. A *risk evaluation* has to be conducted without consideration of costs or other non-risk factors, and must evaluate risks to potentially exposed or susceptible subpopulations that EPA identifies as relevant to the risk evaluation. *Risk assessment* does not necessarily imply all aspects of TSCA risk evaluation as specified under section 6(b)(4)(A).

3 SCIENTIFIC STANDARDS FOR TSCA RISK EVALUATIONS

TSCA requires that, to the extent that EPA makes a decision based on science under TSCA sections 4, 5, or 6, EPA must use certain scientific standards and make those decisions consistent with the best available science and based on the weight of the scientific evidence [15 U.S.C. 2625(h) and (i)]. In addition, TSCA section 6(b)(4) establishes specific substantive requirements for EPA-conducted risk evaluations [15 U.S.C 2605 (b)(4)].

Given these TSCA requirements, EPA recommends that external parties, in preparing a draft risk evaluation, adhere to the same scientific standards and other substantive requirements that apply to EPA in the course of implementing TSCA section 6(b) and preparing risk evaluations. External-party draft risk evaluations will be of little or no value to EPA if they do not explain how they conform to the TSCA provisions mentioned above. Also, although it will be within EPA's purview to determine that the information received meets the TSCA scientific standards, EPA will be more able to effectively utilize the information provided if external parties understand and apply their best judgment in conforming to the standards in draft risk evaluations.

3.1 Best Available Science

EPA recommends that external parties prepare draft risk evaluations using the best available science as described in 15 U.S.C. 2625(h) and defined in 40 CFR Part 702.33, establishing the procedures for chemical risk evaluations under TSCA.

In determining that best available science is an integral component of section 6 risk evaluations, EPA defined, by rulemaking, best available science as "science that is reliable and unbiased. Use of best available science involves the use of supporting studies conducted in accordance with sound and objective science practices, including, when available, peer reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data)."

As defined in 40 CFR Part 702.33, implementing the best available science also means "…to consider, as applicable:

- The extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information;
- The extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture;
- The degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented;
- The extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and
- The extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies or models."

EPA's *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act*, under 40 CFR Part 702.45, require EPA to peer review the risk evaluations. If EPA were to use parts of a draft risk evaluation submitted by an external party, those parts would become part of the EPA's risk evaluation and would undergo the required peer review, regardless of the source of the information.

EPA is not suggesting that external parties need to have their draft risk evaluation peer reviewed before submission to EPA. Therefore, EPA has not described a peer review process for these submissions in this guidance document. However, if an external party wanted to have an assessment peer reviewed before submission to EPA, nothing would preclude those activities and EPA would likely consider any peer review record that was provided with the submission.

3.2 Weight of Evidence

TSCA risk evaluations are required to rely on the weight of the scientific evidence [15 U.S.C. 2625 (i)]. EPA recommends that external parties use weight of the evidence approaches in the draft risk evaluation. In accordance with the final rule (40 CFR Part 702.33), weight of evidence is defined as "a systematic review method, applied in a fit-for-purpose manner, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance."

Application of weight of the evidence analysis is an integrative and interpretive process. It is more than simply tallying of the number of positive and negative studies and is applicable to both human health and ecological risk evaluations.

There are certain principles of weight of the evidence evaluations that are universal, including foundational considerations such as objectivity and transparency, and the general process. This process starts with assembling the relevant information, evaluating the information for quality and relevance, and finally the synthesizing and integrating the different lines of evidence to support conclusions (EPA, 2016). EPA recommends that interested persons explain the evidence integration process and methods used to support the weight of evidence analysis in the draft risk evaluation.

3.2.1 SYSTEMATIC REVIEW

EPA intends to use systematic review when conducting TSCA risk evaluations for existing chemicals. As defined by the Institute of Medicine, systematic review "is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies" (Institute of Medicine, 2011). The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent (Bilotta, Milner, & Boyd, 2014).

The principles of systematic review have been well developed in the context of evidence-based medicine (e.g., evaluating efficacy in clinical trials) (Higgins & Green, 2011) and are being adapted for use across a more diverse array of systematic review questions, including answering important public health questions. The National Academies' National Research Council (NRC) has encouraged EPA to move towards systematic review processes to enhance the transparency of scientific literature review that support chemical-specific risk assessments to inform regulatory decision making (National Research Council, 2011, 2014).

Key elements of systematic review include (Hoffmann et al., 2017; Stephens et al., 2016):

- A clearly stated set of objectives (defining the question)
- Developing a protocol which describes the specific criteria and approaches that will be used throughout the process
- Applying the search strategy criteria in a literature search
- Selecting the relevant papers using predefined criteria
- Assessing the quality of the studies using predefined criteria
- Analyzing and synthesizing the data using the predefined methodology
- Interpreting the results and presenting a summary of findings

EPA/OPPT plans to integrate systematic review into the TSCA risk evaluations to meet the statutory requirements of TSCA. EPA strongly recommends that external parties use systematic review approaches when developing draft TSCA risk evaluations. EPA also recommends that external parties develop a pre-established systematic review protocol at the beginning of the draft risk evaluation development process to ensure that the review is complete, unbiased, reproducible, and transparent. The protocol should describe the pre-specified criteria,

approaches, methods and/or procedures to identify, select, assess, and summarize the findings of studies including strengths, limitations, and relevance of each study. The protocol should also address how the evidence will be integrated, as necessary and appropriate, based upon strengths, limitations and relevance. Expert judgement is often used throughout the process of evaluating the studies. However, benchmarking interpretations to clear criteria for study quality will help improve the transparency and objectivity of the evaluation.

3.3 Data Quality

Prior to developing a draft risk evaluation, EPA recommends that external parties implement a data quality system that ensures that the draft risk evaluation uses quality data intended for risk assessment purposes consistent with the requirements of TSCA [15 U.S.C. 2625(h) and (i); 2605 (b)(4)]. EPA encourages external parties to read EPA's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*. EPA will use the approaches set forth in the rule at 40 CFR Part 702 and the accompanying preamble to prepare the various sections of TSCA risk evaluations. Thus, EPA recommends that external parties familiarize themselves with those documents. In addition, *EPA's Assessment Factors* provides a summary of general assessment factors that the public should consider when generating and documenting the quality of their information products (EPA, 2003). Moreover, EPA strongly recommends that external parties disclose and make publicly available all raw data used to support the draft risk evaluation, if not previously reported in the literature.

4 TSCA RISK EVALUATION PROCESS

Since EPA's inception, human health and ecological risk assessment has informed decisions made to protect humans and the environment. EPA uses risk assessment as a tool to integrate exposure and health effects or ecological effects information into a characterization of the potential for health hazards in humans or other hazards to our environment (U. S. Environmental Protection Agency, 2004).

According to 40 CFR Part 702, the steps of the TSCA risk evaluation process include scope, hazard assessment, exposure assessment, risk characterization and finally a risk determination. The steps are applicable for both human health and environmental risk evaluations and rely on EPA's risk assessment frameworks described in the *Framework for Ecological Risk Assessment* (EPA, 1992a), the *Guidelines for Ecological Risk Assessment* (EPA, 1998) and the *Framework for Human Health Risk Assessment to Inform Decision Making* (EPA, 2014). External parties should consider these frameworks when developing fit-for-purpose draft risk evaluations that are consistent with the best available science and based on the weight of the evidence within the context of TSCA. While EPA is ultimately most interested in the quality of the submitted

external party draft risk evaluation, not the specific process by which the evaluation was developed, EPA believes following these steps help to ensure a high-quality product.

TSCA includes an explicit requirement for EPA to publish the *scope* for any risk evaluation it will conduct. Further, TSCA requires this scope to include the hazards, exposures, conditions of use, and the potentially exposed or susceptible subpopulations that EPA expects to consider. In the TSCA Risk Evaluation Rule (40 CFR Part 702), EPA has included the conceptual model and an analysis plan as required components of the scope for a risk evaluation. As defined in EPA's guidance, problem formulation captures the exposure pathways, receptors and health endpoints that would be included in the risk evaluations (EPA, 1992a; 1998; 2014). Furthermore, EPA's risk assessment frameworks explain that the outcome of problem formulation is a conceptual model(s) and an analysis plan (EPA, 1992a; 1998; 2014). Hence, problem formulation has essentially the same function as scoping under the amended TSCA, thereby aligning the requirements of the scope for a TSCA risk evaluation with the components of a problem formulation in EPA guidance (EPA, 1992a; 1998; 2014). Thus, EPA guidance on problem formulation will be relevant and useful to external parties in scoping TSCA risk evaluations.

TSCA provides that external parties may submit to EPA a draft risk evaluation. EPA does not expect that external parties would provide a separate scope to EPA. However, EPA recommends that external party draft risk evaluations document problem formulation in the form of a conceptual model and analysis plan.

Furthermore, since each risk evaluation is based on the specific circumstances surrounding the chemical being assessed, this guidance does not single out of any specific guidance, method or model for routine use, to ensure that there is flexibility to address the specific questions of the TSCA risk evaluation. When conducting risk evaluations, EPA will take advantage of existing guidance, tools, models and/or approaches that are relevant and available for use in conducting a risk evaluation under TSCA as long as they are consistent with the various requirements of section 26 of TSCA, including conforming to the best available science and weight of the evidence requirements. A compendium of existing guidance typically consulted by EPA can be found at the following websites:

- EPA's *Risk Assessment Portal*
- EPA's *Pesticide Science and Assessing Pesticide Risks*[1]
- EPA's *Predictive Models and Tools for Assessing Chemicals under TSCA*
- OECD's *Assessment of Chemicals*

[1] Some of the risk assessment guidance for pesticides may be useful to address risk assessment issues in TSCA risk evaluations.

4.1 Scope

As stated above, the scoping step of a TSCA risk evaluation identifies the hazards, exposures, conditions of use and potentially exposed or susceptible subpopulations that EPA expects to consider in a risk evaluation. EPA recommends that, in scoping a draft risk evaluation, external parties follow the principles and approaches laid out in 40 CR Part 702 and the accompanying preamble.

In addition, consistent with Part 702, EPA recommends that the outcome of the scoping phase of the draft risk evaluation includes a conceptual model(s) and an analysis plan which are further discussed in 4.1.1 and 4.2.2. In addition, it is also important to identify previous assessments and regulatory history during scoping as this information may frame the draft risk evaluation by understanding (1) what elements of the life cycle of the chemical substance are regulated by EPA, other federal agencies, States, local governments, Tribes and other international organizations; (2) how they are regulated; (3) the rationale for the regulation, and (4) how the chemical substance has been evaluated in the past (e.g., previous risk assessments). Previous assessments generally provide useful information about exposure, hazards and risks and any potentially exposed or susceptible subpopulations that have been considered by others.

4.1.1 CONCEPTUAL MODEL

An important outcome of the scoping phase is a conceptual model that:

- Describes actual or predicted relationships between the chemical substance, the conditions of use and human and environmental receptors.
- Identifies human and ecological health hazards expected to be evaluated in the draft risk evaluation.
- Considers the life cycle of the chemical substance, including manufacture, processing, distribution in commerce, storage, use, and disposal, relevant to the conditions of use expected to be considered in the draft risk evaluation.

The conceptual model also addresses those aspects that might not be analyzed in the draft risk evaluation (e.g., excluded exposure pathways), the recognition of which sometimes is important in the overall decision-making process (EPA, 2014). Additional details and examples are provided in EPA's risk assessment guidance (EPA, 1998; 2014).

4.1.2 ANALYSIS PLAN

The analysis plan describes the analytical intentions for the TSCA risk evaluation (EPA, 2014). During analysis planning, the relationships described in the conceptual model are evaluated to determine how they will be assessed using available and new data. Although the conceptual model may identify a larger set of pathways and relationships, the analysis plan focuses on the pathways and relationships that will be pursued in the risk assessment. The rationale for selecting

or omitting pathways and relationships is incorporated into the plan, as is acknowledgement of data gaps and uncertainties.

The analysis plan may include these components: (1) the assessment design and rationale for selecting specific pathways to include in the risk assessment; (2) a description of the data, information, methods and models to be used in the analyses (including uncertainty analyses), as well as intended outputs (e.g., risk metrics); (3) associated data gaps and limitations. The analysis plan may describe the extent or aspects of the assessment that are qualitative rather than quantitative. In all cases, the analysis plan addresses the quality of data to be used (EPA, 1998; 2014).

4.2 Exposure Assessment

Pursuant to TSCA section 6(b)(4)(F), EPA, "where relevant, will take into account the likely duration, intensity, frequency, and number of exposures under the conditions of use in an exposure assessment". Consistent with TSCA, the exposure assessment evaluates, where relevant, the likely duration, intensity, frequency and number of exposures to human populations (e.g., general population, consumer, worker), including potentially exposed or susceptible subpopulations, and ecological receptors (e.g., aquatic, terrestrial species) for the conditions of use of the chemical substance. TSCA also requires that a risk evaluation describe whether aggregate or sentinel exposures are considered in the exposure assessment and the basis for that consideration.

An exposure assessment includes some discussion of the size, nature, and types of individuals or populations exposed to the chemical substance, as well as discussion of the uncertainties in this information. Exposure can be measured directly, but when data are unavailable, it is estimated indirectly through consideration of measured concentrations in the environment, consideration of models of chemical transport and fate in the environment, and/or estimates of human intake or environmental exposure over time.

Using reasonably available information, exposures are estimated (usually quantitatively) for the identified conditions of use. For human health exposure, the assessment would consider all relevant potentially exposed or susceptible subpopulation(s) and utilize any combination, as available, of population-based epidemiological studies, information related to geographic location of susceptible subpopulations, models representing exposures to the population, measurements in human tissues or relevant environmental or exposure media, and any other relevant, scientifically valid information or methodology. In an environmental health exposure assessment, the interaction of the chemical substance with ecological receptors is characterized and evaluated.

EPA recommends that external parties document all aspects of the exposure scenarios being evaluated in the draft risk evaluation (e.g., workers, general population, consumers). This also

includes documentation for scenarios for relevant potentially exposed or susceptible subpopulations. EPA also recommends that external parties document use of aggregate or sentinel exposure analyses (if applicable). EPA recommends including the following information in the exposure assessment:

- Chemical-specific factors including, but not limited to: physical- chemical properties and environmental fate and transport parameters.
- Characterization of exposure information relevant to exposure scenarios under evaluation including a discussion of the overall quality and main limitations of the exposure data, data sources and underlying principles and assumptions using weight of evidence approaches.
- Disclosure of all data used for the calculations (modeled and measured).
- If applicable, model framework and its scientific basis, including rationale for why the model is selected for risk assessment purposes, utilizes the proper modeling relationships, results in reasonable approximations, and meets the objectives of the evaluation in terms of acceptable levels of uncertainty and variability.
- Discussion of available exposure evidence on factors that may make potentially exposed or susceptible subpopulations more vulnerable to the exposure of the chemical of interest.
- Basis for selecting key and/or supporting exposure studies in the exposure assessment;
- List of equations and explanation of each input and output parameter that are used to calculate the exposure estimates.
- Where relevant, estimates of human exposure by pathway that consider likely duration, intensity, frequency, and number of exposures under the conditions of use under evaluation, including potentially exposed or susceptible subpopulations, in a manner appropriate for the intended risk characterization.
- If considered, aggregate and/or sentinel exposure estimates under the conditions of use and the basis for their estimation.
- Results of the sensitivity analysis when modeling is used (if applicable).
- Integrative discussion based on the best available science and the weight of the evidence. Discussion should include the strengths and limitations of the exposure evidence, along with a discussion on the uncertainties, variability, degree of confidence, and underlying assumptions including science policy assumptions supporting the exposure estimates.

Further discussion of these elements can be found in *EPA's Guidelines for Exposure Assessment* (EPA, 1992b). In addition, EPA encourages interested persons to consult EPA guidance on various issues related to exposure assessment and exposure to susceptible subpopulations. The guidance can be found at *EPA's Risk Assessment Portal*, *Protecting Children's Environmental Health* web page or EPA's *ExpoBox*. Other applicable policy for susceptible subpopulations can be found in Executive Orders *12898* and *13045* and EPA guidance on evaluating health risks to children (1995, 2006).

EPA recommends that external parties use tables, figures, and appendices to increase transparency and clarity of the exposure assessment.

4.3 Hazard Assessment

In compliance with TSCA section 6(b)(4)(F), EPA will conduct a hazard assessment on each chemical substance or category, under the conditions of use as identified by the Administrator. A hazard assessment identifies the types of adverse health or environmental effects or hazards that can be caused by exposure to the chemical substance in question, and characterizes the quality and weight of the evidence supporting this identification.

The hazard assessment has two components: the hazard identification and the dose-response assessment. Hazard identification is the process of determining whether exposure to a chemical substance or category can cause an increase in the incidence of specific adverse health or environmental effects (e.g., cancer, developmental toxicity, reduced growth in aquatic organisms). All hazard information is reviewed in a manner consistent with best available science and weight of the evidence. This includes the identification, evaluation, and synthesis of information to describe the potential health and environmental hazards of the chemical, under the conditions of use, and documentation of all assessment methods.

As part of the hazard identification assessment, EPA typically reviews and summarizes all available and relevant data. Specifically, for human health hazards, the assessment considers all relevant potentially exposed or susceptible subpopulation(s). Potential information sources that may support the health hazard assessment include, but are not limited to: population based epidemiological studies that identify risk factors and susceptible subpopulations; information related to geographic location of subpopulations; models that represent health effects of relevant subpopulation; *in vivo* and/or *in vitro* laboratory studies; and mechanistic or kinetic studies in a variety of test systems including, but not limited to, mode of action (MOA), adverse outcome pathways (AOP)], toxicokinetics, toxicodynamics, and computational toxicology (e.g., high-throughput assays, genomic response assays). The hazard identification will also include an evaluation of the strength, limitations, and uncertainties associated with the available information. Similarly, field or laboratory data and modeling strategies may be used in the environmental hazard assessment.

In some cases, computer models using structure-activity relationships (i.e., predictions of toxicological activity based on analysis of chemical structure) also may be used as supporting evidence for both the human health and environmental hazard assessment. Read-across and chemical category approaches can be used when data gaps occur in the hazard database of the chemical of interest.

Dose-response assessment describes dose-response relationships in the hazard information, in other words how the likelihood and severity of adverse health or environmental effects (the

responses) are related to the amount and condition of exposure to a chemical substance (the dose provided). The same principles generally apply for studies where the exposure is to a concentration of the chemical substance (e.g., airborne concentrations applied in inhalation exposure studies or water or other media concentrations for ecological exposure studies), and the resulting information is referred to as the concentration-response.

EPA recommends that external parties document all aspects of the environmental and human health hazard identification and dose-response assessments including the following information:

- Characterization of nature and severity of human health and ecological effects and their respective dose or concentration responses including a discussion of the overall quality and main limitations of the hazard data, data sources and underlying principles and assumptions.
- Disclosure of all data used for the calculations of hazard values (modeled and measured).
- If applicable, for any model used, the model framework and its scientific basis (e.g., physiologically-based pharmacokinetic modeling), including rationale for why the model is selected for risk assessment purposes, utilizes the proper modeling relationships, results in reasonable approximations, and meets the objectives of the evaluation in terms of acceptable levels of uncertainty and variability.
- Incorporation of mechanistic data, if available, to inform the biological or chemical events associated with toxic effects (i.e., MOA/AOP) and guide the synthesis and integration of the effects evidence for both hazard identification and dose-response.
- Discussion of available hazard evidence on factors that may make potentially exposed or susceptible populations more vulnerable to adverse effects (e.g., life stages, windows of developmental susceptibility).
- If applicable, a discussion of the adequacy and robustness of data-gap filling approaches (e.g., analog data through read-across, category approaches, models based on structure-activity relationships) and basis for use.
- Integrative discussion based on the best available science and the weight of the evidence. Discussion should include the strengths and limitations of the hazard evidence, along with a discussion on the uncertainties, variability, degree of confidence, and underlying assumptions including science policy assumptions supporting the hazard values.
- The correspondence between the expected route(s) of exposure and the exposure route(s) utilized in the studies forming the basis of the dose-response assessment, as well as the interrelationships of potential effects from different exposure routes.
- Model(s) used to develop the dose-response curve and the basis for selecting the model, their strengths and limitations and underlying assumptions.
- Extrapolation methods and the basis for selecting them, including their strengths and limitations and underlying assumptions.
- The basis for selecting interspecies dose scaling factors to account for extrapolating doses from experimental animals to humans.

- Rationale for route-to-route extrapolations, including strengths and limitations
- Discussion if the dose-response values are adopted from other sources (e.g., EPA's Integrated Risk Information System (IRIS) assessments).
- Applicability of dose-response values (i.e., point of departures) and critical effects to susceptible populations,
- Basis for selecting key and/or supporting studies and corresponding human health and ecological hazards (or effects) including their basis and hazard values for pertinent exposure scenarios.
- List of equations and explanation of each input and output parameter that are used to calculate the hazard values.
- Major assumptions and uncertainties in the dose-response values affecting their confidence.
- Basis for the selection of uncertainty factors for estimating hazard values for the variety of scenarios under examination.

EPA's Weight of Evidence in Ecological Assessment may provide useful information for planning and using the weight of the evidence for the ecological component of the hazard assessment (EPA, 2016). EPA recommends that external parties use tables, figures, and appendices to increase transparency and clarity of the human health and environmental hazard assessments.

4.4 Risk Characterization

According to EPA's Risk Characterization Handbook, "*the risk characterization integrates information for the preceding components of the risk assessment and synthesizes an overall conclusion about risk that is complete, informative, and useful for decision makers*" (EPA, 2000). It should be prepared according to the *Risk Characterization Principles* of transparency, clarity, consistency and reasonableness (EPA, 2000).

- *Transparency* ensures that any reader understands all the steps, logic, key assumptions, limitations, and decisions in the risk evaluation, and comprehends the supporting rationale that lead to the outcome (EPA, 2000).
- *Clarity* ensures that the risk characterization is clear and easy to understand (EPA, 2000),
- *Consistency* ensures that the content of the risk characterization is in harmony with statutory requirements, program precedents, and EPA's assessment guidelines including science policy, and deviations are explained if need be (EPA, 2000).
- *Reasonableness* ensures that the integrative analysis of the risk characterization is scientifically sound and based on the best available science by following an acceptable logic and retaining common sense in applying relevant guidance (EPA, 2000).

EPA recommends that external parties develop a risk characterization section that addresses the following:

- Discussion of the risk estimation approach, including equations and pertinent assumptions.

- Discussion of how the hazard and exposure assessments are integrated into the quantitative and/or qualitative estimates of risk for the identified human and ecological receptors under the conditions of use of the chemical substance (e.g., exposure scenarios, hazard values and rationale for their selection, effects of concern based on weight of evidence approach).

- Summary of the magnitude of the human health and environmental risk estimates (in tabular form) for the various exposure scenarios assessing the conditions of use of the chemical substance, including risk estimates for aggregate or sentinel exposures (if applicable).

- Discussion of the major issues associated with determining the nature and extent of the risk in potentially exposed or susceptible populations, including data needs.

- Discussion of the overall characterization and/or analysis of the impact of the uncertainty and variability on estimated risks. This should include considerations regarding uncertainty and variability in each of the risk evaluation components (e.g., use of default assumptions such as uncertainty factors, exposure scenarios, choice of models and information used for quantitative analysis). It should also include discussion about data quality issues in the data/information supporting the risk characterization and the level of confidence in the human health and environmental hazard and exposure values used to estimate risks.

- If appropriate and relevant, discussion of plausible alternative interpretations of the data and analyses used in the draft risk evaluation.

5 RISK DETERMINATION IN TSCA RISK EVALUATIONS

The final step of a risk evaluation is for EPA to determine whether the chemical substance, under the conditions of use, presents an unreasonable risk of injury to health or the environment. Determinations will specify whether a chemical substance does or does not present an unreasonable risk of injury to health or the environment under the conditions of use. In general, EPA may weigh a variety of factors in determining unreasonable risk and include, but not limited to: the effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects on the chemical substance on the environment and environmental exposure under the conditions of use; the population exposed (including any susceptible populations); the severity of hazard (the nature of the hazard, the irreversibility of hazard); and uncertainties.

TSCA expressly reserves to EPA the final determination of whether risk posed by a chemical substance is "unreasonable." External parties have the option of including their unreasonable risk judgment in their draft risk evaluation, with the clear understanding that EPA reserves the authority to determine and issue the final determination.

6 REFERENCES

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