Risk Assessment Forum Plan: To develop an EPA *Framework for Dose-Response Assessment for Human Health Risk Assessments to Inform Decision Making*

Summary: The product of this activity will be a document describing the framework in which EPA conducts dose-response assessments for human health risk assessment to inform Agency decision making. This framework document will describe EPA's overall approach and key considerations for dose-response assessment for all categories of health effects (including cancer and other effects). It will reflect the recommendations emphasized in *Science and Decisions* (NRC, 2009) that EPA's risk assessments be supported by both scientific and risk management considerations. Accordingly, some methods and considerations described in the framework document may be illustrated by referencing existing assessments conducted in a variety of EPA risk management contexts. In addressing the EPA's broad array of risk management needs, the EPA framework differs from the dose-response framework described in *Science and Decisions*.[1] Accordingly, to reduce confusion, it is not labeled with the same "unified" descriptor.

In describing EPA's approach to dose-response assessment, the framework document will emphasize two principles around which dose-response assessments for all categories of health effects are organized. The first organizing principle is that the dose-response assessment is expected to build on and reflect the underlying evidence base[2] for the agent[3] being assessed and associated conclusions regarding mode of action (MOA). The phrase MOA is used broadly in this document and is intended to refer to MOA as described in the Cancer Guidelines, as well as, the concepts represented by "adverse outcome pathways" (AOP) and other concepts that at their core emphasize organization and interpretation of the available evidence to inform hazard, dose-response and risk characterizations (USEPA, 2005; Ankley et al., 2010; Edwards et al., 2016). The second organizing principle is that the assessment approach is expected to fit the purpose[4] for which it is conducted (e.g., support a risk assessment to inform a decision on adequacy of a national standard or on cleaning -up a contaminated waste site). Together, these principles insure that Agency risk assessments are scientifically sound and fulfill the decision-making needs for which they are conducted.

In responding to *Science and Decisions*, the framework document will publicly communicate that, as supported by the scientific data and called for by the decision context, EPA in some instances uses predictive risk approaches for endpoints other than cancer, as well as for cancer. The document will additionally recognize that there continues to be a role at EPA for an array of dose-response tools and approaches. For example, there are regulatory and community-based decision constructs that use RfCs and RfDs in a way that facilitates EPA health-protective decision

[1] While the EPA framework, like that described in *Science and Decisions* (e.g., *Science and Decisions,* Figure 5-8), assigns a prominent role to consideration of the evidence base and biological understanding of the stressor, the EPA framework, in identifying the dose-response approach and metric(s) to be developed, also gives prominence and an up-front role to risk management needs (and "fit for purpose"), which was emphasized in the *Science and Decisions* recommendations on planning and problem formulation for risk assessments.

[2] The evidence base may be comprised of underlying data from human, experimental animal and mechanistic studies.

[3] The term "agent" refers generally to any chemical substance, mixture, or physical or biological entity being assessed, unless otherwise noted (USEPA, 2005, and other Agency guidance/guidelines).

[4] The concept, "Fit for Purpose" (based on attention to planning, scoping and problem formulation), is emphasized in the *Framework for Human Health Risk Assessment to Inform Decision Making* (USEPA, 2014).

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making. There are also situations, however, where RfCs and RfDs may be insufficiently informative to the decision, and other types of approaches supported by the evidence base are needed.[5] Although Agency experience with predictive risk assessments for noncancer endpoints may be limited (outside of risk assessments for the national ambient air quality standards), more activity in this area is recently being created by strong datasets, new techniques and decision-making needs.

While this framework document will describe key considerations in dose-response assessment for human health risk assessment at EPA, the framework document is envisioned as being relatively concise (20-100 pages) and aimed at clarifying these core aspects ("not too in the weeds"). Additionally, while it will cite relevant, existing Agency documents, it will not be repetitive of existing documents. This framework is envisioned to reflect key considerations emphasized in other existing frameworks, such as, the linking exposure and effects information illustrated in the framework for ecological risk assessment (Attachment 1). Consistent with the *Framework for Human Health Risk Assessment to Inform Decision Making* (USEPA, 2014), the framework document will also recognize the important role of planning, scoping and problem formulation in informing the assessment design and associated outputs or dose-response metrics.

As one method for illustrating the variety of assessment approaches implemented in various EPA risk management contexts and aspects of the framework, the framework document will cite existing Agency documents as case studies. Examples of such case studies include assessments conducted for specific programs to inform specific risk management decisions, such as assessments involving agents for which the MOA for carcinogenicity is nonlinear or for which exposures of interest overlap with the exposures at which effects are observed. The general expectation is that the document would include short descriptions of the case studies and cite more detailed Agency documentation. The case studies will be identified and their descriptions developed in collaboration with the Human Health Oversight Committee (HHOC). To the extent that any case studies identified involve methods development work (e.g., *de novo* case studies) this work, as appropriate, will occur as part of this project.

Background: *Science and Decisions* recommended that EPA phase in a "unified" framework for dose-response assessment, referring to a "common analytic framework regardless of type of outcome" (NRC, 2009).[6] The RAF's initial efforts in consideration of the NAS recommendations on dose-response assessment included focused discussions at the 2010 Colloquium. Based on recommendations from the colloquium, a RAF technical panel developed an Exposure-Response Matrix (Attachment 2) that recognizes the various factors influencing EPA's dose response assessment approaches, including the type of data and the breadth and robustness of the database, as well as, the environmental decision-making purpose.

Following the initial RAF efforts, the STPC's NRC Risk Assessment Reports Workgroup (WG) suggested that EPA's response to this NRC recommendation[7] should be to emphasize the different types of dose-response analysis needed to suit EPA's different decision-making contexts and purposes for conducting an assessment, as recognized in the Exposure-Response Matrix. The STPC WG also emphasized that biological understanding (*e.g.*, MOA) based on the available

[5] Judgments on the extent to which different approaches are supported by the evidence base will necessarily depend on the risk management context and associated decision.

[6] Chapter 5 of Science and Decisions includes the full NRC discussion on this topic (NRC, 2009).

[7] Excerpts on this topic from the 2014 STPC NRC Workgroup Report , which include excerpts from *Science and Decisions* unified dose-response recommendations, are provided in Attachment 3.

database is integral to decisions on the type and key aspects of the dose-response analysis to be pursued. Furthermore, the WG emphasized the importance of a variety of approaches to meet the needs of different risk assessment types and recognized the variability in resource availability, in addition to the differences in depth of the underlying database.

The activities suggested by the STPC WG were condensed into a multi-step activity proposed to the STPC. This activity included the development of case studies "to explore and develop a 'unified dose-response framework' that extends the 'data-first, defaults second' paradigm and use of the MOA/AOP framework from the Cancer Guidelines to non-cancer endpoints." With STPC concurrence for beginning the activity, a RAF technical panel produced a scoping document for the case study activity.[8] Consideration of the draft scoping document and suggested case studies led the RAF to conclude that additional planning work in this area was needed. In this same timeframe, the STPC also recommended that the overall multi-step activity be reorganized and streamlined.

More recently, a subgroup of the HHOC was formed to reflect on EPA activities to date in this area and propose a revised plan for RAF activities. In developing this proposed plan, the subgroup thoughtfully reflected on EPA activities while considering the recommendations from *Science and Decisions*, current EPA risk assessment activities and needs, appropriate objectives for RAF activities in this area at this time, and critical aspects of the path forward on these activities.

Important Aspects of Framework Document: This dose-response framework document will recognize several important aspects of EPA's dose-response assessments that relate to the integral role of MOA considerations and/or to the 'Fit for Purpose' emphasis.

- Agents the Agency assesses may pose risks of an **array of effects** (*e.g.*, cancer, respiratory, and developmental).
- The EPA has a **variety of uses for dose-response assessments** (*e.g.*, "routine" and screening-level risk assessments for varying programmatic needs (regulatory and otherwise), and benefits analyses). Different types of assessments for these different uses reflect the Agency's implementation of the "fit for purpose" concept and the corollary that one size does not fit all situations. In all situations, however, EPA guidance specifies both a clear, sound scientific basis and development of the assessment via a transparent, documented process.
- The assessment **approach reflects the risk management decision needs, policy options and available information**. There is a relationship among these considerations because the type of decision that can be made is to some extent a function of the robustness of the underlying database for the agent being assessed, which influences the kind of dose-response assessment that can be developed. Resource availability and timeline can also influence the type of approach adopted.
- The EPA performs assessments for **agents that differ in various aspects of underlying evidence base**, including the
    - extent of our knowledge about their **MOA**;

[8] Another related activity has involved review of the state of the science with respect to quantifying human variability for purposes of deriving reference values or risk-specific doses and how quantitative estimates of human variability have been or could be used in deriving reference values for human health risk assessment at EPA, as well as consideration of future research needs in these areas. The document for this activity is nearing the external peer review phase.

- make up of the evidence base (e.g., relatively more/less comprised of laboratory **animal *in vivo*, *in vitro/in silico*/lower taxa, controlled human studies, epidemiology**), as well as quality or robustness of the database;
- extent of our knowledge about variation in susceptibility across **human lifestages** (prenatal through elderly adult); and,
- type of **key health endpoints** (*e.g.*, cancer, neurological, reproductive, developmental)**.**

Health effects information may be organized using various paradigms (*e.g.*, Attachment 4).

- **Different dose-response models** may be appropriate depending on extent of knowledge on agent toxicity, effects and MOA, context/purpose for assessment, need for extrapolation from the range of exposures at which effects have been observed to environmental exposures of interest.
- There is **human variability** in the response(s) assessed and dose-response approaches may differ in how and to what extent they include **quantitative estimates** of this variability due to differences in the purpose for the assessment and in the associated database.
- Differences in **human lifestages** (e.g., related to physiology) may contribute to differences in response to the assessed agent(s).
- **Additional sources of exposure to the same or similarly acting agent(s)** may influence response to the assessed agent(s) (e.g., as compared to **"background"**). Dose-response approaches may vary in how and to what extent they consider this influence due to differences in the purpose for the assessment and the associated database data.
- **Health/disease status/background of exposed population** may influence the response to the assessed agent(s). Dose-response approaches may vary in how and to what extent they consider this influence due to differences in the purpose of the assessment and the associated database.

Accordingly, rather than a one-size-fits-all approach, the framework document will recognize that the type of dose-response analyses employed in an EPA risk assessment vary depending on risk management needs, the extensiveness and robustness of the available information, as well as the extent of understanding on how the agent elicits health effects (*e.g.*, MOA).[9] The document will recognize existing approaches,[10] as well as, efforts underway now and expected in the future that will contribute to new methods and approaches. These efforts may contribute to a range of approaches, from more refined analyses in cases with supporting biological understanding to screening methods that take advantage of the breadth of new information types, including, as one example, high throughput approaches.

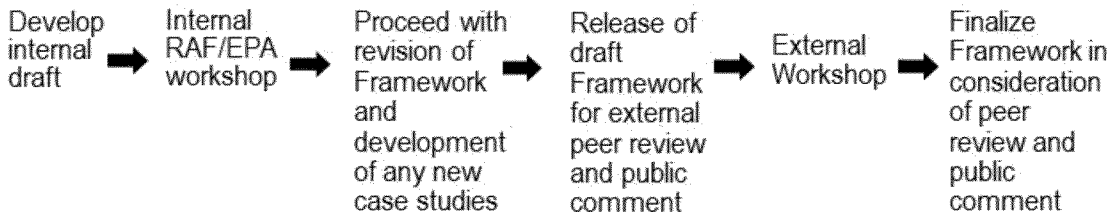
[9] MOA is central to dose-response assessment decisions and approaches as reflected in the Cancer Guidelines emphasis on MOA, which informs both WOE on hazard characterization and the dose-response assessment approach.

[10] Examples are provided in Attachment 6.

[11] All Agency guidelines specify certain default options/assumptions. For example, where the observed range is above the exposure range of interest, the Cancer Guidelines specify that, where sufficient data are available, a biologically-based model may be used. In the absence of data supporting a biologically based model for extrapolation outside of the observed range, the MOA analysis determines the approach used, with a linear extrapolation approach used when the MOA is supportive of linearity or is not understood (USEPA 2005, pp. A-8). EPA's guidelines for reproductive, neurological, developmental toxicity risk assessment generally recognize

Instead of establishing or prescribing new approaches or default assumptions,[11] this framework document is intended to specify that EPA's dose-response assessment approaches reflect the underlying database and associated biological understanding of physiological response to the agent being assessed. For example, it will recognize that in assessments for which exposures of interest are appreciably below the range of the dose-response data, the choices made with regard to the approach used for characterization of the dose-response relationship for those exposures may be influenced by MOA, as well as the decision-making context and risk management needs.

Major Steps In Document Completion: The major steps for completion of this document are summarized here.



These steps include an internal Agency workshop or colloquium, which is intended to facilitate intra-Agency consideration of the initial draft document and the achievement of Agency consensus on the final document. The colloquium will coincide with the internal review period for the draft document to facilitate internal review of the document, and consideration of the availability of and/or need for additional case studies. Development of descriptions for new case studies will proceed coincident with revision of the framework document to address internal review comments. Following internal review and subsequent revisions, the document with associated case studies will be released for external peer review and public comment. A public colloquium will be held to encourage discussion, comment and familiarity of external stakeholders with the framework.

Timeline for Major Milestones:

Sept/Oct 2016 – STPC approval of this plan to develop a document describing EPA's framework for dose-response assessment for human health risk assessments that inform decision making, with accompanying case study descriptions (e.g., summaries in appendix).

Nov 2016 – Assembly of Technical Panel (8-10)

Technical Panel will be comprised of technical staff reflecting relevant expertise in major programs, and a region, as well as expertise with ORD. This Panel will develop the framework as described here and is also expected to have responsibility for associated case studies. Any "de novo" case studies identified in the course of the framework document development for inclusion in this activity will be developed by a smaller team overseen by this Technical Panel. Joint Technical Panel and HHOC meetings will be held on occasion to facilitate common understanding of key issues.

an assumption of a nonlinear dose-response relationship, citing the existence of capacities for damage repair, compensation mechanisms, etc. (USEPA, 1991, 1996, 1998). The *Guidelines for Mutagenicity Risk Assessment* emphasize use of the "most appropriate extrapolation models … guided by the available data and mechanistic considerations" (USEPA, 1986, pp. 2-7, 2-8).

Nov 2016 – Kick-off meeting for Technical Panel (1-day, in-person).

Summer 2017 - Draft framework document in HHOC review.

Sept/Oct 2017 – Internal EPA workshop on framework document (with associated case study summaries).

May 2018 - External review draft framework document (with associated case study summaries), released for scientific peer review and public comment

Summer 2018 – Public Workshop on draft framework. Solicit ideas on subsequent pieces/modules (*e.g.*, methods/guidance on specific analysis areas).

Oct-Dec 2018 – Final framework document (with associated case study summaries) released.

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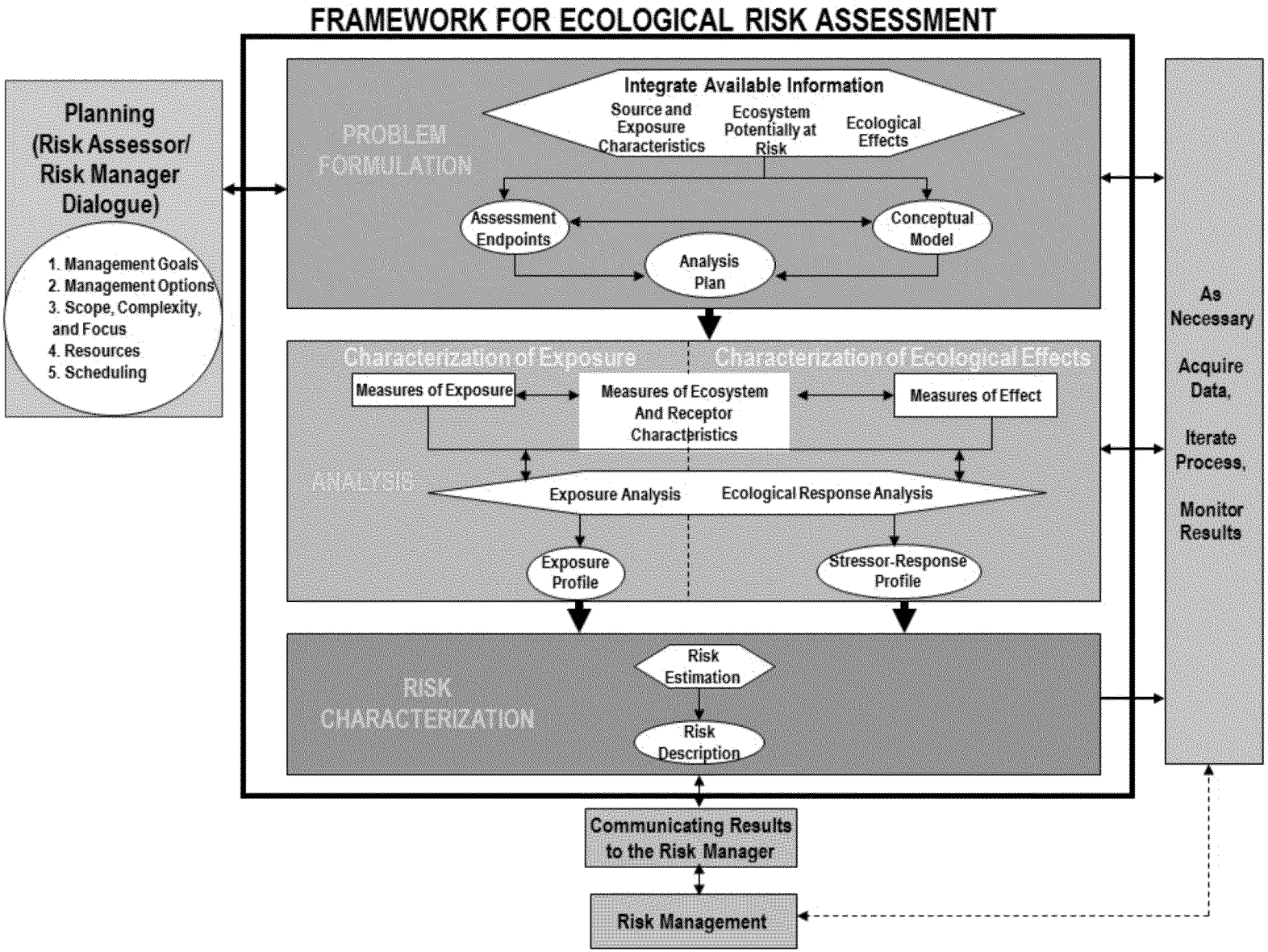
Additional Background Materials (Available for Review upon Request)

1. Internal Final - STPC NRC Risk Assessment Reports Workgroup Plan (2014) and Issue Paper on Unified D-R
2. Science and Decisions – Summary and Unified Dose Response Chapter (NRC, 2009)
3. RAF Progress on Unified Dose Response
   a) Internal Final - Dose Response Matrix (2013)
   b) Internal Draft - State of the Science Review on Human Variability (2016)
   c) Case Studies Scoping – Charge (3/2/2015)

d) Internal Draft - Case Studies Scoping Report (2016)

e) Internal Draft - Case Studies Framework (2016)

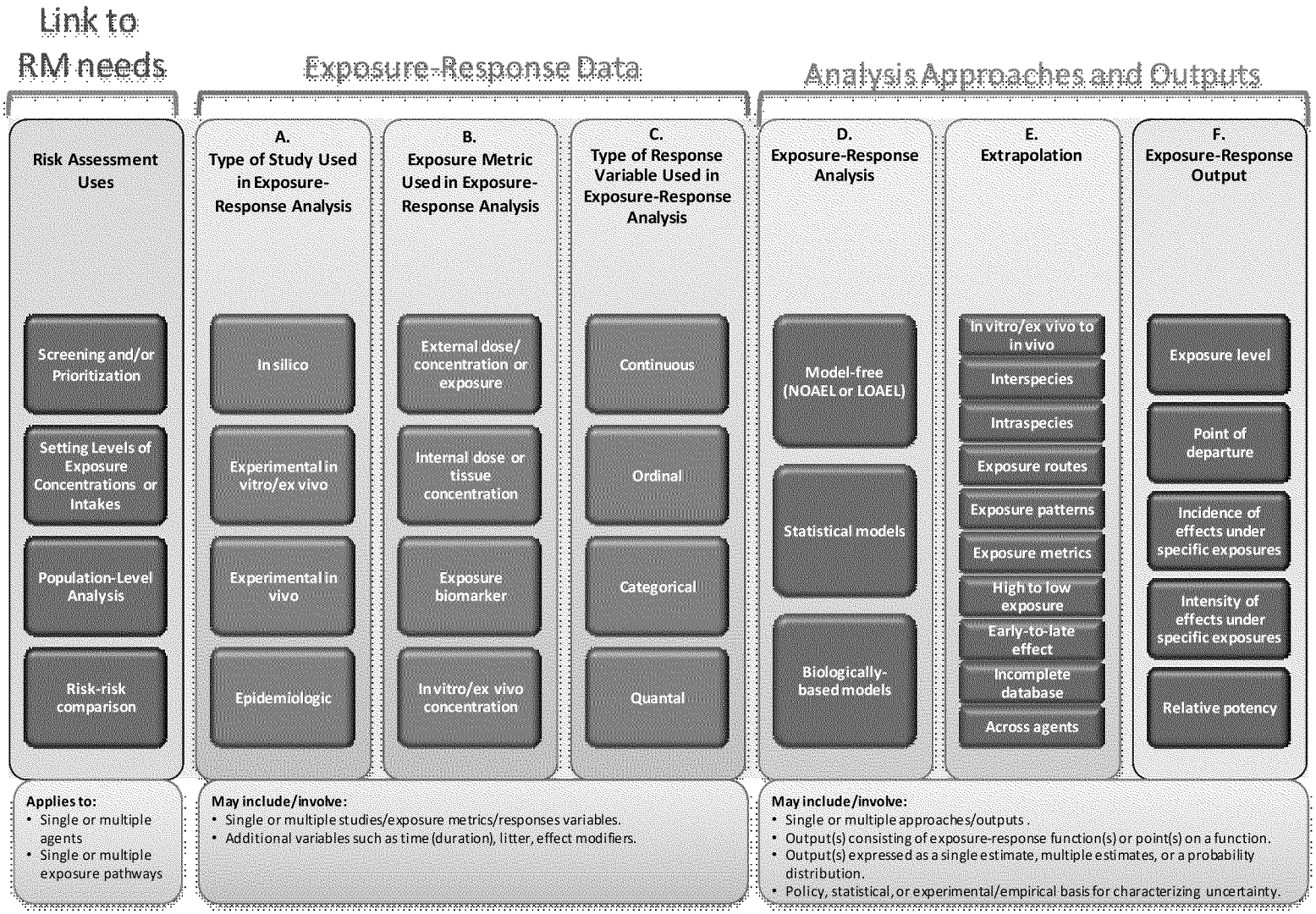
4. 2010 RAF Human Health Risk Assessment Colloquium Report (2012) and Action Plan for Advancing Human Health Risk Assessment (2011)
5. Risk Assessment for Benefits Assessment: Framework for Analysis of a Thyroid-Disrupting Chemical (Journal of Toxicology and Environmental Health, Axelrad et al 2005) and other associated documents
6. Guidance Document of Evaluating and Expressing Uncertainty in Hazard Characterization (IPCS 2014), A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects (Environmental Health Perspectives, Chiu and Slob 2015) and other associated documents
7. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolations Factors for Interspecies and Intraspecies Extrapolation.



Attachment 1.

Attachment 2.

Exposure-response Matrix



Attachment 3. Excerpts from June 23, 2014 internal deliberative "NRC Risk Assessment Reports Workgroup: Report to the Science and Technology Policy Council." This full report summarized the STPC NRC Workgroup considerations and recommendations on the 10 categories of NRC recommendations from four reports: (1) Toxicity Testing in the 21st Century: A Vision and a Strategy (2007); (2) Phthalates and Cumulative Risk Assessment: The Task Ahead (2008); (3) Science and Decisions: Advancing Risk Assessment (2009): and (4) Exposure Science in the 21st Centurey: A Vision and a Strategy (2012). The STPC NRC Workgroup first developed category-specific discussion papers (titled Issue Papers) that considered the NRC recommendations, Agency policies, approaches and activities related to the recommendations and options for further Agency activities or projects in the various category(ies) of recommendations. The Issue Papers described Agency context for each category, providing a framework for identifying options for further projects. Drawing from the Issue Papers, the broader report presented the NRC recommendations and projects proposed by the workgroup for all 10 categories of recommendations. Further details on Agency approaches, activities and responses related to the unified dose-response recommendation are presented in the "Issue Paper on Unified Dose-Response (Category 3) For NRC Risk Assessment Reports Workgroup."

Unified Approach to Dose-Response Assessment – Category 3

3.1 NRC recommendations

Chapter 5 of *Science and Decisions* is entitled "Toward a Unified Approach to Dose-Response Assessment." The key conclusions presented in this chapter address limitations in current dose-response assessment methods. The NRC concluded that "Separation of cancer and noncancer outcomes in dose-response analysis is artificial…The separation not only is scientifically unjustified but leads to undesirable risk-management outcomes, including inadequate attention to noncancer end points, especially in benefit-cost analyses."

The NRC went on to say that "The underlying scientific and risk-management considerations point to the need for unification of cancer and noncancer approaches in which chemicals are put into a common analytic framework regardless of type of outcome. There are core differences among endpoints, but in this analytic framework a dose corresponding to a specified increase in risk in the population could be derived for both cancer and noncancer end points, and this would add transparency and quantitative insight to risk-management decisions."

A unified dose response approach will need to consider all lifestages. With respect to early lifestage considerations for risk of cancer, the NRC said in *Science and Decisions* that "EPA needs methods for explicitly considering in cancer risk assessment *in utero* exposure and chemicals that do not meet the threshold of evidence that the agency is considering for judging whether a chemical has a mutagenic mode of action."

The NRC then made the following recommendations:

- The committee recommends that EPA implement a phased-in approach to consider chemicals under a unified dose-response assessment framework that includes a systematic evaluation of background exposures and disease processes, possible vulnerable populations, and modes of action that may affect human dose-response relationships.
- The reference dose (RfD) and reference concentration (RfC) should be redefined to take into account the probability of harm.
- In developing test cases, the committee recommends a flexible approach in which different conceptual models can be applied in the unified approach.

Full implementation of the NRC recommendations at this time would involve a substantial change to conduct of EPA's human health risk assessments. The Workgroup's proposed near-term activities for unified dose-response are intended to further explore a unified approach to dose-response assessment and to develop methods and data sets needed for implementing a unified approach.

The proposed activities involve improved integration of data at different levels of biological organization (i.e., cell, organ, individual, population) to advance the biological understanding of how interaction of a chemical at the target site may lead to adverse health effects in the diverse human population and across different lifestages, and translating that biological understanding into a quantitative assessment that can unify cancer and non-cancer approaches. Progress on advancing biological understanding, through further development and application of the Mode of Action (MOA)/Adverse Outcome Pathway (AOP) framework, needs to be made in tandem with progress on more sophisticated quantitative approaches (including probabilistic and other methods for quantitative treatment of uncertainty and variability) and on generating the necessary data. Finally, as emphasized in the EPA *Framework for Human Health Risk Assessment to Inform Decision Making* it is important to recognize that different types of dose-response analyses will be suitable for different decision contexts.

3.2 Key ongoing and completed activities

The RAF has prepared a draft "Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Inter-Species and Intra-Species Extrapolation" (DDEFs Guidance). The document is expected to be completed in Summer 2014.

The RAF is preparing a draft paper on chemical additivity, which updates EPA methods for dose-response assessment of chemical mixtures. This document is part of the RAF's activities on cumulative risk assessment. External peer review of the document is expected in 2014.

The RAF recently initiated two dose-response State of the Science reviews:

- Methods and Data for Quantitatively Estimating Variability in Human Biological Responses from Exposure to Chemicals
- Approaches and Methods for Estimating Incidence of Health Effects as a Function of Exposure.

3.3 Workgroup's proposed activities

The Workgroup selected eight proposed activities on dose-response assessment for the high-priority group, including the three ongoing RAF activities listed above and one new activity to be initiated in the near term. The remaining four proposed activities depend on information developed in the ongoing and near-term activities, and thus would be initiated in the future. These activities will be used to apply the MOA/AOP construct/framework analysis approach both qualitatively and quantitatively; will encompass a diverse range of chemicals and with diverse data sets; cover multiple lifestages (including addressing the NRC's early life carcinogenicity recommendations; also see the section of the implementation plan for the Prenatal category), and will fulfill a diverse range of risk assessment needs, from screening/prioritization to population-level analyses.

Ongoing Risk Assessment Forum activities with high priority

- Activity 3-1: Complete the DDEFs Guidance document.
- Activity 3-2: Continue and complete the paper on chemical additivity.
- Activity 3-3: Continue and complete the dose-response State of the Science reviews.

New activity to be initiated in the near-term

- Activity 3-4: Perform diverse case studies to explore and develop a "unified dose-response framework" that includes extension of the "data-first, defaults second" paradigm and use of the Mode of Action/Adverse Outcome Pathway (MOA/AOP) framework from the Cancer Guidelines to non-cancer endpoints.

New activities to be initiated in the future

The remaining proposed activities would be conducted in sequence, following the completion of the case studies (Activity 3-4) described above.

- Activity 3-5: Perform additional case studies to evaluate how applying a unified dose-response framework would affect development of programmatic and regional risk assessments, as well as risk management decisions based on those assessments.

- Activity 3-6: Develop/update data needed for implementation of the specific elements of proposed quantitative approaches (both probabilistic and non-probabilistic) as part of a unified dose-response framework.

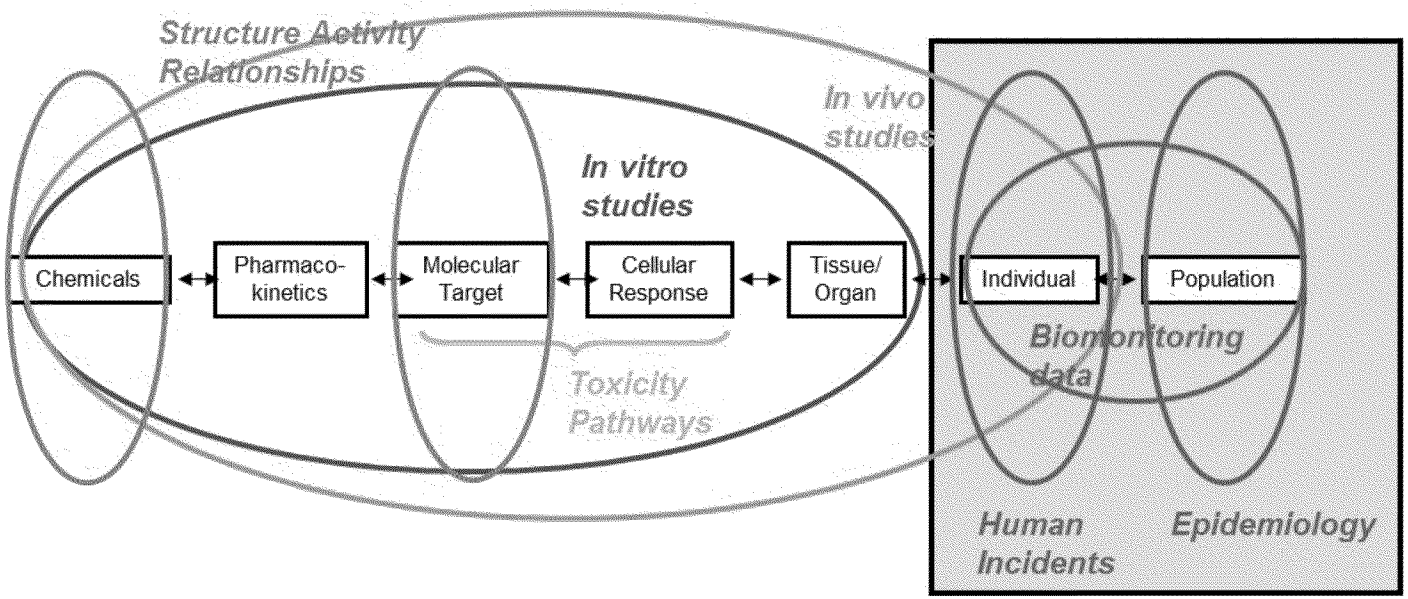
  Some elements of this activity will be addressed by the RAF State of the Science review listed above (Activity 3-3) and by the proposed activity for updating/evaluating support for explicit defaults (Category 4).

- Activity 3-7: Based on lessons learned from case studies and State of the Science reviews, prepare draft guidance that describes biological data interpretation across the Agency using a unified dose-response construct/framework analysis approach that is applicable to any endpoint or adverse outcome, and any degree of data availability.

- Activity 3-8: Develop a training program for agency risk assessors so that the unified dose-response framework is applied in a consistent manner across the Agency.

Attachment 4

Source to Effects Pathway, Adapted from NRC, 2007



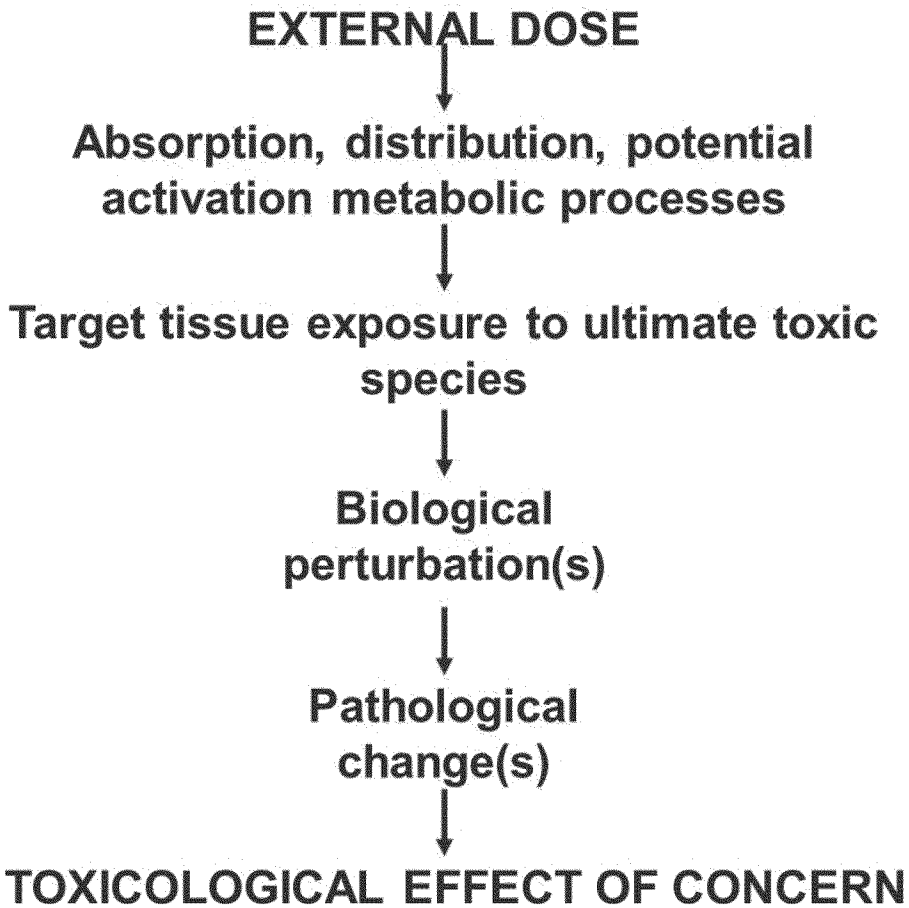
Adverse Outcome Pathways

Greater Toxicological Understanding ⟷ **Greater Risk Relevance**

9

Attachment 4 (continued)

Generic Set of Key Events in a MOA, Adapted from Boobis, et al (2009)



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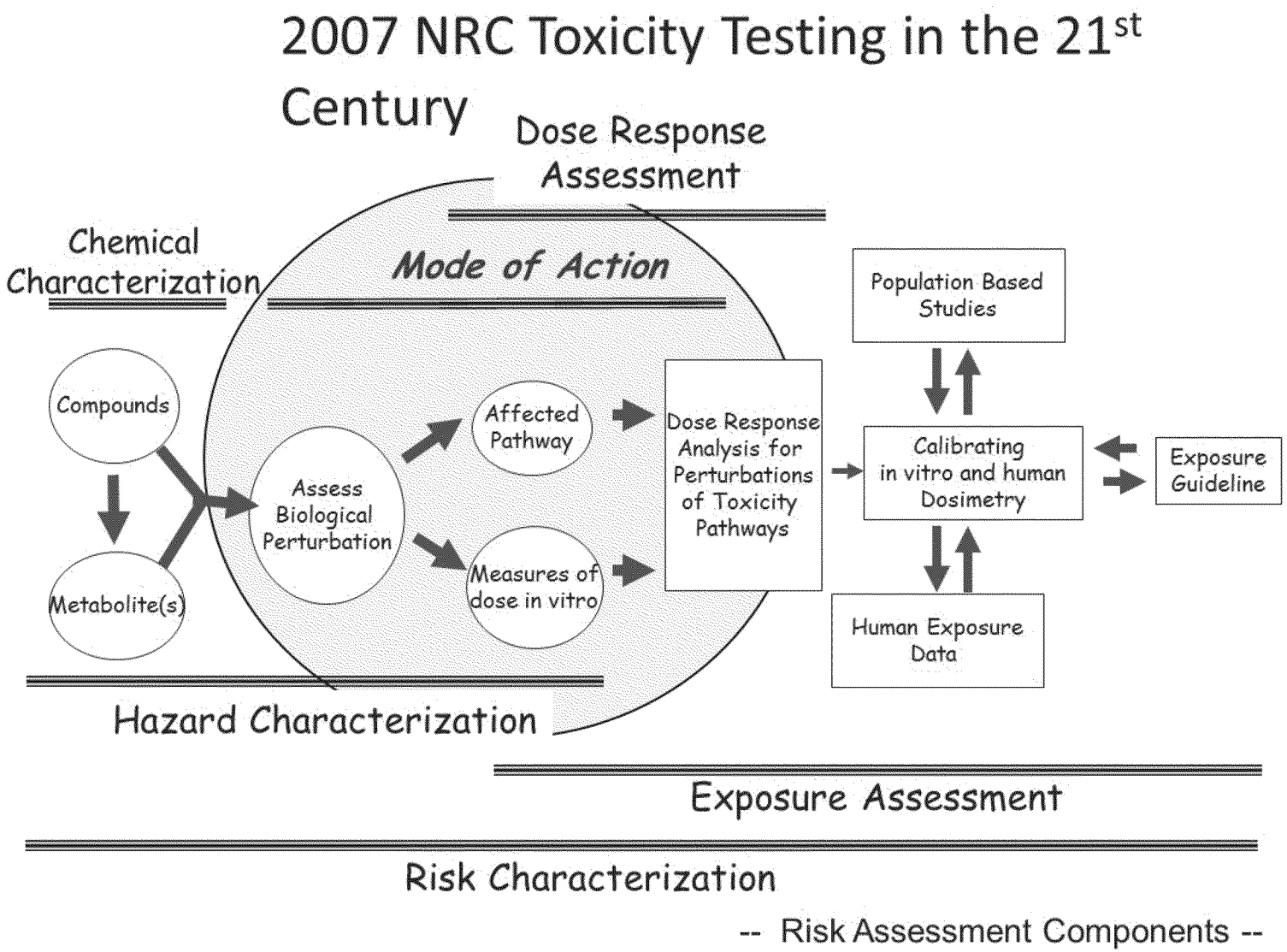

Attachment 5. Existing EPA approaches for dose-response assessment and characterization (examples of entries in Exposure-Response Matrix).

D-R Product	**Description and Notes** (e.g., strengths and limitations/needs)
Approaches that extrapolate to exposures below range where effects observed	
RfC/RfD	Estimate of exposure concentration/dose "without appreciable risk of deleterious effects" in sensitive subgroups over a lifetime - Useful for judging situations of little risk and has established role in some risk management decision frameworks (e.g., helps identify situations where would not consider additional action) - Risk characterization of higher exposures would be helpful in some risk management decisions
Cancer URE/slope factor	Upper bound estimate of cancer risk at low doses
Approaches focused on the range of observations	
Exposures generally appreciably lower than those at which effects observed	
POD	(OPP)
Relative potency factors or toxicity equivalence factors	This approach is generally based on MOA characterizations and the factors are developed using comparisons of experimental dose-response data.
Exposures commonly overlap with those at which effects observed	
C-R functions	(NAAQS) Used to provide best estimate of risk for at-risk populations, accompanied by variability and uncertainty characterization. Depending on available information, may also include risk estimates based on upper/lower probable estimates. Focus is most commonly population risk.
Health-based benchmarks	(NAAQS) These are used with exposure assessments to characterize risk to at-risk populations (e.g., CO, ozone).
Exposures lower than or overlapping with those at which effects observed	
Quantitative hazard screening *[Different such approaches belong here or in group below]*	*QSAR/Read Across (*Quantitative Structure Activity Relationship analysis, Category Formation or Chemical Groupings, and Read-Across) use existing information for chemicals with similar properties or effects to determine potential human health and ecological hazard when data are lacking., *TTC* (Threshold of Toxicological Concern) approach has been used in the assessment of some data-limited chemicals by other organizations but not by EPA; *Qualitative or Semi-quantitative* approaches describes hazard, dose-response, and description of uncertainties without providing a reference value has been done in IRIS when database not sufficient for reference value derivation.