



Science and Science Policy Foundation for IRIS Assessments

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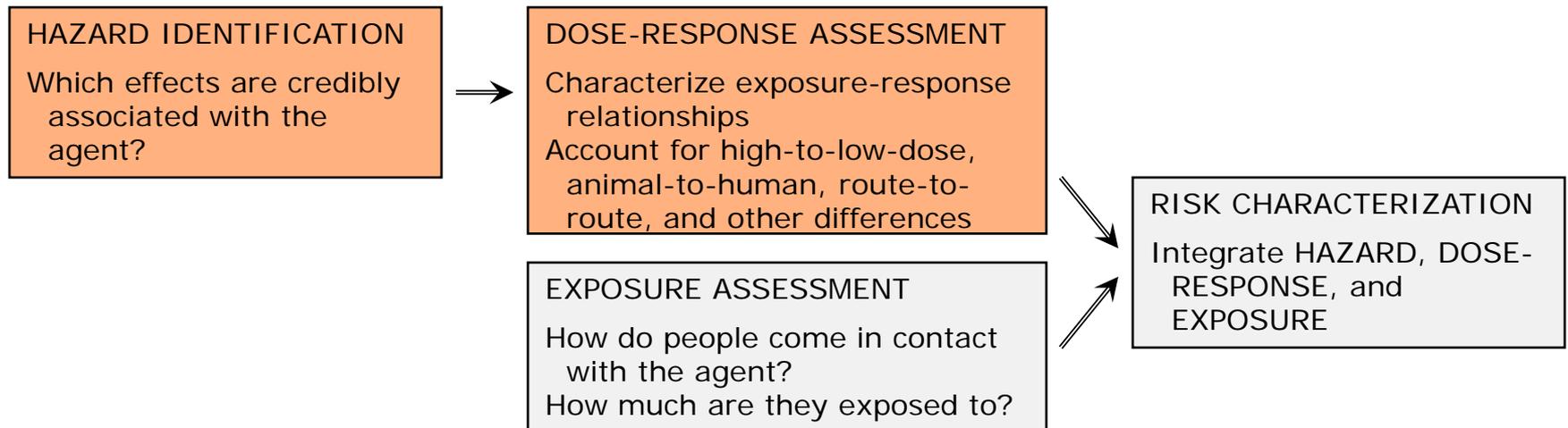
Overview

- IRIS Program overview
- Ongoing NRC reviews
- Science and IRIS assessments
- Role of the SAB CAAC in moving forward



IRIS Program Overview

- IRIS assessments critically review publicly available peer-reviewed studies to:
 - Identify adverse health effects
 - Derive toxicity values





IRIS Program Overview

- IRIS is the only federal public program that provides toxicity values for both cancer and noncancer effects.
- There are currently more than 550 chemicals on the IRIS database.
- As stand-alone scientific documents, IRIS assessments are hazard assessments, not risk assessments or regulatory decisions.
- Scientific integrity, expert peer review, and transparency are cornerstones of the IRIS Program.



IRIS Program Overview

- IRIS assessments have no direct regulatory impact until they are combined with other information (extent of exposure to people, cost of cleanup, available technology, etc.) to inform actions and decisions.
- IRIS is used by:
 - EPA program and regional offices.
 - State and local health agencies.
 - Other federal agencies.
 - International health agencies.



Types of Studies Available for Various Chemical Agents

	Pharmaceuticals	Pesticides	Criteria air pollutants	IRIS chemicals
Randomized control trials	Required	--	--	--
Guideline-based animal studies	Required	Required	Sometimes	Sometimes (e.g., NTP)
Epidemiology studies at ambient exposure levels	--	Sometimes	Yes (extensive)	Sometimes
Other epidemiology studies	Post-market surveillance	Sometimes	Yes	Sometimes
Other animal studies	Sometimes	Sometimes	Yes	Usually

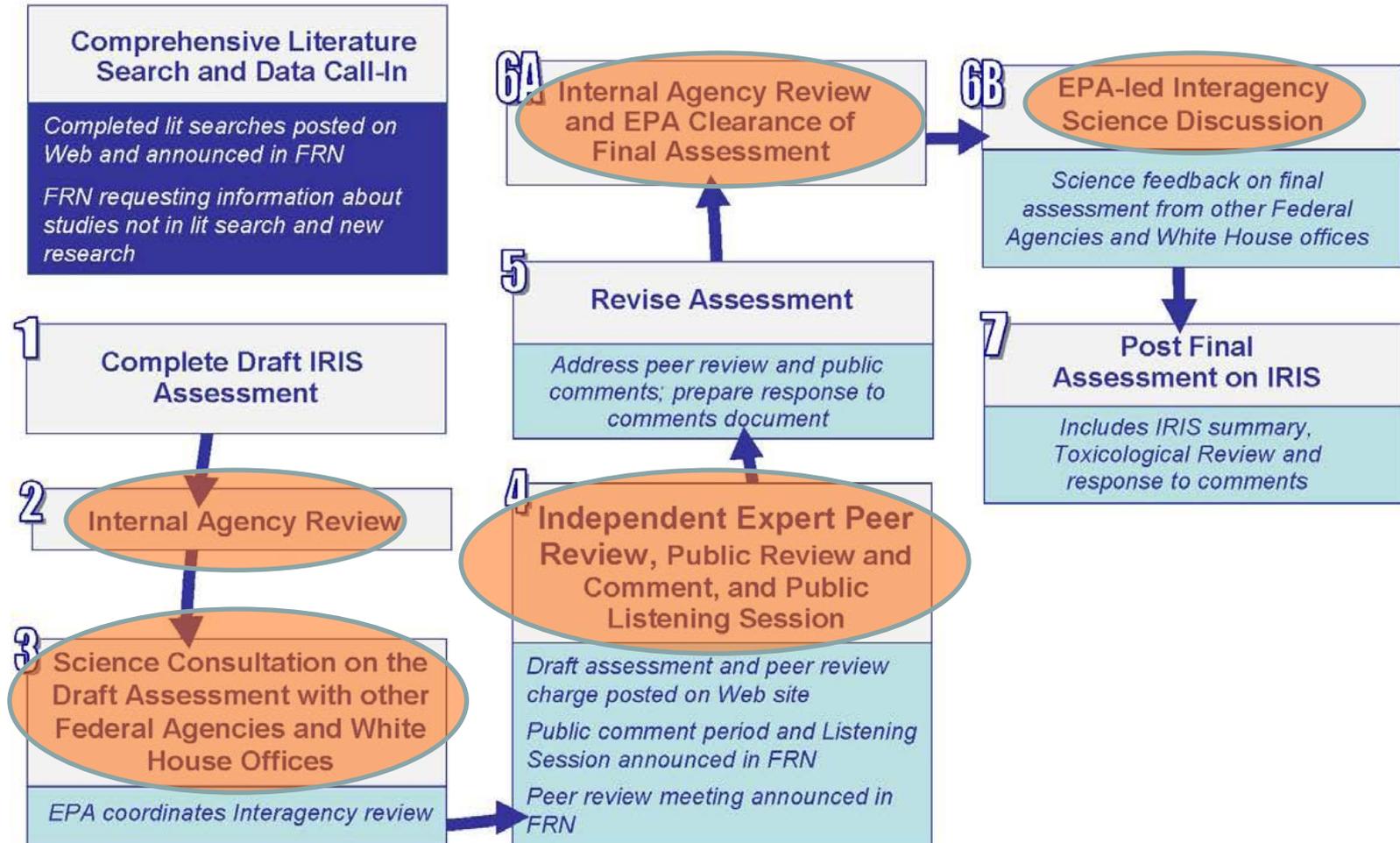


EPA's Programs and Regions Make Decisions About Potential Risks

- Results from epidemiological and animal studies generally need to be extrapolated to inform risk management:
 - Clean Air Act specifies "an ample margin of safety to protect public health."
 - Safe Drinking Water Act specifies "no adverse effects on the health of persons may reasonably be anticipated to occur, allowing an adequate margin of safety."
 - Cancer decisions often consider a range of risks between 1/10,000 and 1/million.
- It is not feasible to always wait for new studies.
- The process should promote assessments that:
 - are completed in a reasonable time;
 - use a reasonable level of resources;
 - can use the data at hand.



The IRIS Process Provides for Multiple Levels of Scientific Review



Innovation with Health and Environmental Research Online (HERO) Database

- HERO – a database of scientific studies used to develop EPA health assessments
 - Created for the Integrated Science Assessment Program.
 - Expanded to include IRIS assessments.
 - Allows the public to readily access studies on which decisions are based.
- HERO provides:
 - Citation and abstract.
 - Topic areas that describe the reference.
 - Project pages so that information considered in an assessment can be viewed.
- HERO is an **EVERGREEN** database – new studies are continuously added.

The screenshot shows the HERO database website interface. At the top, there's a navigation bar with the EPA logo and links for 'LEARN THE ISSUES', 'SCIENCE & TECHNOLOGY', 'LAWS & REGULATIONS', and 'ABOUT EPA'. Below this is a search bar and a 'Public access to the scientific literature used for EPA's science assessments' banner. The main content area is divided into sections: 'The HERO Database' (describing its purpose), 'EPA's Recent Assessments' (highlighting the 2010 IRIS Toxicological Review of Ethylene Glycol Monobutyl Ether), and 'Browse Topics in HERO' (with dropdown menus for 'Air Pollutants', 'Chemicals & Substances', and 'Health & Environmental Effects'). A 'Quick Finder' section provides links to various assessment portals. A sidebar on the right offers 'Top Three Questions', a 'Search HERO' section, and 'Evaluating Scientific Literature'.

www.epa.gov/hero

Recent Accomplishments

Final assessments recently posted:

Tetrahydrofuran (February 2012)

Dioxin, noncancer (February 2012)

Tetrachloroethylene (February 2012)

Dichloromethane (November 2011)

Trichloroacetic acid (September 2011)

Trichloroethylene (September 2011)

Hexachloroethane (September 2011)

Urea (July 2011)

Assessments recently released for public comment and external peer review:

1,2,3-, 1,2,4- and 1,3,5-Trimethylbenzenes (June 2012)

Ammonia (June 2012)

Biphenyl (September 2011)

Vanadium pentoxide (September 2011)

n-Butanol (August 2011)

1,4-Dioxane, inhalation (August 2011)

Libby amphibole asbestos (August 2011)



Some Assessments in the IRIS Pipeline

acrylonitrile
ammonia
arsenic (inorganic)
benzo[a]pyrene
biphenyl
t-butanol
chromium VI
1,4-dioxane (inhalation)
ETBE

ethylene oxide (cancer)
formaldehyde
Libby amphibole asbestos
methanol (noncancer)
PAH mixtures relative potency
factors
PCBs (noncancer)
RDX
trimethylbenzenes



NRC Review of Inorganic Arsenic IRIS Assessment: Public and Partner Engagement

Sep 2012 - EPA internal scoping/problem formulation workshop.

Jan 8-9, 2013 – EPA-led public stakeholder workshop.

Jan 24-25, 2013 – NRC-led public scoping/problem formulation meeting.

Next Step, April 4-5, 2013 NRC-led science issues workshop.



NRC Review of the IRIS Assessment Development Process

- NRC is conducting a review of the IRIS assessment development process:
 - April 2011 - NRC provided recommendations for improving the development of draft IRIS assessments in its report on the IRIS formaldehyde assessment.
 - April 2012 - NRC began:
 - 1) a review of the IRIS assessment development process with respect to changes that have been made or are planned to address the 2011 recommendations, and
 - 2) a review of current methods for evidence-based analyses.



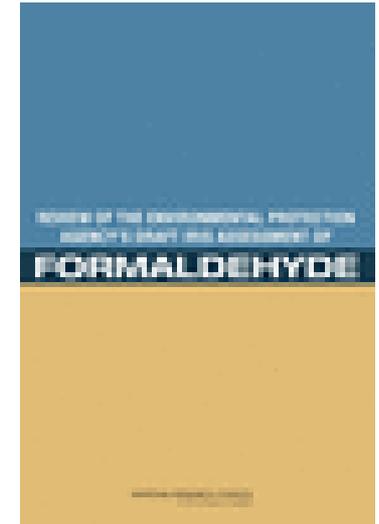
NRC Review of the IRIS Assessment Development Process

- NRC convened public meetings in Sep and Dec 2012.
- In Jan 2013, NCEA submitted materials to the NRC regarding the status of implementation of the NRC's recommendations and chemical-specific examples (e.g., draft preamble, draft IRIS handbook).
- March 27-28, 2013 NRC-led Workshop on Weight of Evidence.
- Additional information can be found at:
<http://epa.gov/iris/iris-nrc.htm> or
<http://www8.nationalacademies.org/cp/projectview.aspx?key=49458>



Summary of 2011 NRC Recommendations for IRIS

- The NAS recommended that EPA rigorously edit and streamline documents, use standardized evidence tables, and more clearly articulate methods, criteria and rationales.
- The NAS did not tell EPA to stop developing IRIS assessments or to stop the IRIS Program until changes were fully implemented.



IRIS embraces all of the NRC recommendations and is implementing them.



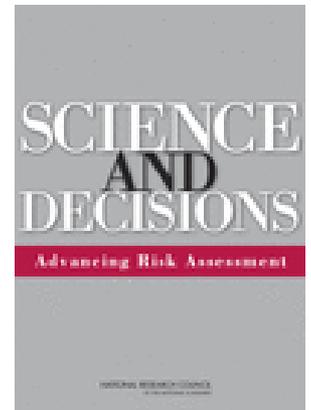
2011 NRC Recommendations for Developing IRIS Assessments

- Provide a fuller discussion of the methods of the assessment; concise statements of criteria used to exclude, include, and advance studies for hazard evaluation and derivation of toxicity values.
- Clearly articulate the rationale and criteria for screening studies and rationale for selecting studies used to calculate toxicity values.
- Use standardized evidence tables to provide methods and results of studies for all health outcomes.
- Use uniform approaches to evaluate strengths and weaknesses of all critical studies and summarize findings in tables.
- Ensure that weight-of-evidence descriptions indicate the various determinants of weight to promote understanding of what elements were emphasized in synthesizing evidence
- Rigorously edit documents to reduce the volume of text substantially and address redundancies and inconsistencies.



Longer-Term 2011 NRC Recommendations for Hazard Identification and Dose-Response Assessment

- Systematic identification of relevant evidence
- Criteria for evaluating the strength of the evidence
- Language for describing the strength of the evidence of causation
 - Standardized to avoid ambiguity
 - Comparable among different agents and outcomes
- Unify dose-response framework
 - Cancer assessments should reflect variability and uncertainty
 - Noncancer assessments should reflect probability of response
- Combine information from multiple studies
 - Should be unusual to use only one study
 - Consideration of meta-analyses





The Path Forward for Implementing the 2011 NRC Recommendations

- The NRC recognized that the changes would involve a multiyear process and extensive effort.
- The IRIS program is taking a phased approach for implementation:
 - Phase 1 focuses on a subset of the shorter-term recommendations for assessments near the end of the document development process or close to final posting.
 - Phase 2 focuses on all of the shorter-term recommendations.
 - Phase 3 will include the longer-term recommendations involving systematic review and evidence integration.
- The path forward will involve continual development and improvement.



General Steps in the Development of an IRIS Assessment

- Literature search and search strategy.
- Selection of critical studies.
- Evaluation of mode of action information.
- Synthesis of hazard information, including susceptible populations and lifestages.
- Selection of studies and endpoints for dose-response modeling for cancer and noncancer – informed by analysis of mode of action data, if available.
- Application of uncertainty factors (1,3,10).
- Analysis of uncertainty.



USEPA Risk Assessment Guidelines

- Guidelines for Carcinogen Risk Assessment (2005).
- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (2005).
- Guidelines for Neurotoxicity Risk Assessment (1998).
- Guidelines for Reproductive Toxicity Assessment (1996).
- Guidelines for Developmental Toxicity Risk Assessment (1991).
- Guidelines for Mutagenicity Risk Assessment (1986).
- Guidelines for the Health Assessment of Chemical Mixtures (1986).
- Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (2000)
- Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (1994).
- Benchmark Dose Technical Guidance (2012).



USEPA Risk Assessment Forum Technical Reports

- A Review of the Reference Dose and Reference Concentration Processes (2002).
- Recommended Use of Body Weight $3/4$ as the Default Method in Derivation of the Oral Reference Dose (2011).
- A Framework for Assessing Health Risks of Environmental Exposure to Children (2006).
- Alpha₂-Globulin: Association with Chemically-Induced Renal Toxicity and Neoplasia in the Male Rat (1991).
- Assessment of Thyroid Follicular Cell Tumors (1998).



Key Features of USEPA Cancer Guidelines

- Analyze data before invoking default options.
- Framework for mode of action.
- Weight-of-evidence narrative for human cancer potential replaces the previous alpha-numeric classification system.
- Two-step dose-response process separates:
 1. modeling the observed data, from
 2. extrapolation to lower doses.
- Linear and nonlinear extrapolations are considered.
- Differential risks to susceptible populations and life-stages are considered.
- Characterization of qualitative and quantitative uncertainty.
- Evaluation of mutagenicity as a mode of carcinogenic action.
- Application of age-dependent adjustment factors (1,3,10) for early-life susceptibility for chemicals with a mutagenic mode of action.



Issues Related to the Use of MOA Data

- Defining a key event.
- Data needed to support a MOA for qualitative and quantitative purposes.
- Data needs for determining a mutagenic MOA.
- Incorporating high throughput and other newer types of data into MOA analyses.



Weighing the Overall Evidence of Each Effect

- For cancer, EPA uses standard descriptors to characterize the weight of the evidence:
 - *Carcinogenic to humans*
 - *Likely to be carcinogenic to humans*
 - *Suggestive evidence of carcinogenic potential*
 - *Inadequate information to assess carcinogenic potential*
 - *Not likely to be carcinogenic to humans*
- For effects other than cancer:
 - EPA will develop uniform language to describe the strength of evidence for noncancer effects.
 - There will be workshops on this topic, including one organized by the NRC.



Low-Dose Extrapolation for Cancer (Cancer Guidelines, 2005)

Linear extrapolation from the POD is appropriate when:

- the agent has a mutagenic mode of action or acts through another mode of action expected to be linear at low doses,

or

- the data do not establish the mode of action, **as default option.**

Nonlinear extrapolation from the POD is appropriate when:

- *there is no evidence of linearity, and*
- *there is sufficient information to support a mode of action that is nonlinear at low doses.*



Scientific Advances in the IRIS Program

- Qualitative and quantitative use of mode of action data in noncancer and cancer assessments.
- Routine use of benchmark dose modeling.
- Evaluation and use of PBPK models for extrapolating from animals to humans and across routes of exposure.
- Accounting for life-stage and subpopulation susceptibility in uncertainty factors.
- Use of data-derived uncertainty factors.
- Characterization of uncertainty in noncancer and cancer analysis.
- Use of time-to-tumor modeling and other advanced modeling for cancer assessments.



A Changing Landscape...

- The risk assessment landscape is evolving:
 - High-throughput technologies, computational toxicology, systems biology and bioinformatics.
 - Genomics and epigenetics
 - Need to understand cumulative risk
 - New regulatory schemes that will provides reams of data

- IRIS assessments will need to evolve with new science.



Cross-Cutting Science Issues

Applying systematic review and integration of evidence.

Accounting for endogenous levels of chemicals.

Use of MOA data.

Use of default assumptions.

Biological adversity of endpoints.

Determination of response levels for PODs.

Use of toxicogenomics and high throughput data.

Determination of male rat kidney-specific effects.

Use of brief exposures during critical windows of development for chronic reference values.

Consideration of controversial tumor outcomes in animals.

Low-dose extrapolations and population risks.

Combining study/dataset information (e.g., averaging, meta-analysis).

Characterizing uncertainty.



The Plan Forward for Assessments

- Continual evolution of the implementation of NRC (2009,2011) recommendations.
- Scientific controversies fully presented in assessments.
- Robust charge presented to peer review panels.



The Role of the SAB CAAC in the Path Forward for the IRIS Program

- Independent peer review of IRIS assessments.
- Feedback on the implementation of the NRC (2009, 2011) recommendations.
- Continuity in reviews across multiple assessments.
- Evaluation and recommendations for complex scientific issues.



Summary

- IRIS is important for informing actions to protect public health – by EPA and other health agencies.
- EPA is implementing all recommendations from the NRC Formaldehyde review – assessments will evolve as EPA receives peer review advice.
- IRIS assessments are consistently becoming:
 - clearer
 - more concise
 - more systematic



General Questions for Consideration

- **What information is needed by the committee to provide a sufficient foundation for the committee’s deliberation and review functions?**
- NRC (2011) indicated that the introductory section of IRIS assessments needed to be expanded to describe more fully the methods of the assessment. NRC stated that they were “not recommending the addition of long descriptions of EPA guidelines to the introduction, but rather clear, concise statements of criteria used to exclude, include, and advance studies for derivation of [toxicity values].” **Please comment on whether the new Preamble provides a clear and concise description of the guidance and methods that the EPA uses in developing IRIS assessments.**
- NRC (2011) provided comments on ways to improve the presentation of steps used to generate IRIS assessments and indicated key outcomes at each step, including systematic review of evidence, hazard identification and dose-response assessment. **Please comment on the new IRIS document structure and whether it will increase the ability for assessments to be more clear, concise and easy to follow.**
- NRC (2011) stated that “all critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated” and that “strengthened, more integrative, and more transparent discussions of weight of evidence are needed.” NRC also indicated that the changes suggested would involve a multiyear process. **Please comment on EPA’s success thus far in implementing these recommendations.**