SBA Environmental Roundtable
IRIS Program Developments

Robert Fensterheim
Nancy Beck
February 22, 2013
Very Recent IRIS Developments

IRIS Program continues to evolve and be a significant focus of attention

– Much of the impetus is driven by NRC/NAS Chapter 7 Roadmap presented in their review of draft IRIS Formaldehyde

• Feb 1: Chemical Assessment Advisory Committee, membership announced
  –  http://yosemite.epa.gov/sab/sabpeople.nsf/WebCommitteesSubcommittees/Chemical%20Assessment%20Advisory%20Committee

• Feb 5: 2013 Work Plan announced
  – 14 substances, includes 3 isomers of trimethylbenzene

• NRC/NAS Review of IRIS Process
  (Board on Environmental Studies and Toxicology (BEST) Committee)
  – Next (3rd meeting), March 27-29 (Washington, DC)
  – NRC Workshop on Weight of Evidence (March 27-28)
Review of IRIS Process

Meeting Information

Project Title: Review of the IRIS Process
PIN: DE5-BEST-11-04
Major Unit: Division on Earth and Life Studies
Sub Unit: Board on Environmental Studies & Toxicology
RSO: Martin, Ellen
Subject/Focus Area: Environment and Environmental Studies

3rd Review of the IRIS Process Meeting
March 27, 2013 - March 29, 2013
National Academy of Sciences Building
2100 C St. NW
Washington D.C.

If you would like to attend the sessions of this meeting that are open to the public or need more information please contact:

Contact Name: Craig Philip
Email: cphilip@nas.edu
Phone: 202-334-1942
Fax: 202-334-2752

Agenda:
This meeting will include a workshop on weight of evidence on March 27-28th that is open to public. However, there is limited space, and you will need to register in advance to reserve your seat. Please email your contact information to Craig Philip at cphilip@nas.edu to register.

The agenda for this meeting is currently being finalized and will be posted soon.
EPA Implementation of NAS Recommendations

In Feb 2013, EPA submitted to NRC materials describing their implementation of “Chapter 7” Recommendations

• Part I: Status of Implementation of Recommendations
• Part 2: Chemical-Specific Examples
• NRC charge includes:
  • “The panel will review the IRIS process and the changes being made or planned by EPA and will recommend modifications or additional changes as appropriate to improve the process, and scientific and technical performance of the IRIS Program.”
Process Changes

Ken Olden, NCEA Director, has been spearheading process changes to the overall program with emphasis on:

– Stakeholder engagement
– Increased transparency, and
– Using the best available science
Public Engagement During Draft Development

New Initiatives to increase dialogue between stakeholders and the IRIS Program during draft development

- November 2012, Olden convened general, well attended, Stakeholder meeting to introduce some of the process changes:
  - Increased use of “public peer consultation workshops” to focus on science issues
    - One of the first anticipated to be: Relevance of mouse lung tumors; applicable to naphthalene, styrene, and ethylbenzene.
  - Public dialogue meetings to discuss available data and science issues for IRIS assessment during draft development
    - Jan 2013, public meeting on Inorganic arsenic
  - Hold a workshop in Spring 2013 on incorporating Systematic Review into the lit search/study selection process
2009 IRIS Process Flow Chart

Assessment Development Process for New IRIS

1. Complete Draft IRIS Assessment
2. Internal Agency Review
3. Science Consultation on the Draft Assessment with other Federal Agencies and White House Offices
4. Independent Expert Peer Review, Public Review and Comment, and Public Listening Session
5. Revise Assessment
6A. Internal Agency Review and EPA Clearance of Final Assessment
6B. EPA-led Interagency Science Discussion
7. Post Final Assessment on IRIS

- Comprehensive Literature Search and Data Call-In: Completed lit searches posted on Web and announced in FRN. FRN requesting information about studies not in lit search and new research.
- Internal Agency Review: Address peer review and public comments; prepare response to comments document.
- Independent Expert Peer Review, Public Review and Comment, and Public Listening Session: Draft assessment and peer review charge posted on Web site. Public comment period and Listening Session announced in FRN. Peer review meeting announced in FRN.
- EPA-led Interagency Science Discussion: Science feedback on final assessment from other Federal Agencies and White House offices.
- Post Final Assessment on IRIS: Includes IRIS summary, Toxicological Review and response to comments.
IRIS Track Milestones

1. Draft Development (hazard identification)
2. Release lit search and Evidence Tables
3. Draft Development (dose-response analysis)
4. Agency Review
5. Interagency Science Consultation
6. Public Comment Period
7. External Peer Review
8. Final Agency Review/Interagency Science Discussion and Posting Final Assessment

2/22/2013
Milestone Changes

• Combining the final two steps - review and posting - into one
• Expanding the public comment period and peer review process into two
• Splitting Draft Development into Hazard Identification and Dose Response Analysis
# Comparison Chart

<table>
<thead>
<tr>
<th>2009 Step</th>
<th>2013 Milestone</th>
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<tbody>
<tr>
<td><strong>0:</strong> Comprehensive Literature Search &amp; Data Call-In</td>
<td>Draft Development (Hazard Identification)</td>
</tr>
<tr>
<td><strong>1:</strong> Complete Draft IRIS Assessment</td>
<td>Release Lit. Search &amp; Evidence Tables</td>
</tr>
<tr>
<td><strong>2:</strong> Internal Agency Review</td>
<td>Draft Development (Dose-Response Analysis)</td>
</tr>
<tr>
<td><strong>3:</strong> Science Consultation on the Draft Assessment w/Other Federal Agencies &amp; White House Officials</td>
<td>Agency Review</td>
</tr>
<tr>
<td><strong>4:</strong> Independent Expert Peer Review &amp; Comment; Public Listening Session</td>
<td>Interagency Science Consultation</td>
</tr>
<tr>
<td><strong>5:</strong> Internal Agency Review &amp; EPA Clearance of Final Assessment; EPA-Led Interagency Science Discussion</td>
<td>Public Comment Period</td>
</tr>
<tr>
<td><strong>6:</strong> Final Agency Review/Interagency Science Discussion</td>
<td>External Review</td>
</tr>
<tr>
<td><strong>7:</strong> Post Final Assessment on IRIS</td>
<td>Final Agency Review/Interagency Science Discussion</td>
</tr>
</tbody>
</table>

**Chemicals:**
- Inorganic arsenic
- ETBE
- RDX
- t-Butanol
- Formaldehyde
- Methanol
- Benzo[a]-pyrene
- Ethylene oxide
- Ammonia
- Trimethylbenzenes
- 1,4-Dioxane (inhalation)
- Biphenyl

2/22/2013
IRISTrack Example: Inorganic Arsenic

### IRISTrack Detailed Report

**Arsenic, inorganic Assessment Milestones and Dates**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Projected Start Date *</th>
<th>Projected End Date *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft Development (hazard identification)</td>
<td>FY03/2nd Quarter</td>
<td>FY13/2nd Quarter</td>
</tr>
<tr>
<td>Draft Development (dose-response analysis)</td>
<td>FY13/2nd Quarter</td>
<td>TBD **</td>
</tr>
<tr>
<td>Agency Review</td>
<td>TBD **</td>
<td>TBD **</td>
</tr>
<tr>
<td>Interagency Science Consultation</td>
<td>TBD **</td>
<td>TBD **</td>
</tr>
<tr>
<td>Public Comment Period</td>
<td>TBD **</td>
<td>TBD **</td>
</tr>
<tr>
<td>External Peer Review</td>
<td>TBD **</td>
<td>TBD **</td>
</tr>
<tr>
<td>Final Agency Review/Interagency Science Discussion and Posting Final Assessment</td>
<td>TBD **</td>
<td>TBD **</td>
</tr>
</tbody>
</table>

* For EPA, the Fiscal Year (FY) starts in October and ends in September of the following year. First quarter runs from October through December; the second from January through March; the third from April through June; and the fourth from July through September.

** To be determined.
Status of EPA Implementation

• New Document Structure – IMPLEMENTED
• The IRIS Assessment Preamble – IMPLEMENTED
• New Initiatives to Improve Overall Process, Quality Control, and Documentation – IN PROGRESS
• Identifying and Selecting Pertinent Studies – IN PROGRESS
• Evaluating and Documenting the Quality of Individual Studies – IN PROGRESS
• Evidence Tables: IMPLEMENTED
• Integration of Evidence for Hazard Identification – IN PROGRESS
• Selection of Studies for Dose-Response Analysis – IMPLEMENTED
• Considerations for Combining Data for Dose-Response Modeling – IN PROGRESS
• Conducting and Documenting Dose-Response Modeling and Deriving Toxicity Values - IMPLEMENTED
• External Peer Review Enhancements - IMPLEMENTED
Part I

• New Initiatives to Improve Overall Process, Quality Control and Documentation: In Progress
  • New instructions for contractors
  • 2011 Chemical Assessment Support Teams (CASTs) within EPA
    • Provides a forum for problem solving;
    • Ensures appropriate disciplinary structure of assessment teams;
    • Pinpoints key issues early on in the assessment;
    • Identifies overarching assessment issues that require Program-wide discussions;
    • Increases objectivity in assessment decisions;
    • Monitors progress in implementing NRC’s 2011 recommendations;
    • Assists in responding to Agency, interagency, external peer review, and public comments;
    • Ensures consistency across assessments; and
    • Serves as a mechanism for documenting and communicating decisions.

• Comment Tracker Database under development
Appendix A: Toxicological Review Template

- Shows new format
- Will list authors, support team, contractors
- Preface will note other existing assessments by National and International Health Agencies
- Hazard Groupings by broad endpoints
- Executive Summary: bottom line values, confidence ratings for non-cancer

- What appears to be missing: Any explicit mention of Mode of Action (MOA), human relevance. Unclear where this will fit in.
Appendix B: Preamble

• Unclear if public comments have been considered and/or incorporated

• Does not appear to be significantly different from the Ammonia or TMB preambles. Unclear if any public comments have been addressed.

• Is not assessment specific, but is general regarding approaches the Agency may use.

• NRC did not necessarily ask for this preamble, NRC asked for “..clear concise statements of criteria used to exclude, include and advance studies for derivation of the RfCs and unit risk estimates”
Appendix C: Direction to Contractors

- Section addresses only dose-response modeling of animal bioassays from standard designs. Notes that analysis of epidemiological studies requires specialized methods documented on a case by case basis.
- Describes basic approach including:
  - conversions to standard units for dosing
  - dose adjustments depending on exposure period
  - BMD approaches/ modeling
  - Survival rate adjustments
  - Organization by broad health effect type (organ system)
  - Use of PBPK models: need for review by experts before using, many specific details here
  - Modeling cancer endpoints for single and multiple tumor types
  - Time to tumor analysis
  - Multivariate Response data, Categorical Regression, and others
# Appendix D: Comment Tracker Database

<table>
<thead>
<tr>
<th>Database ID #</th>
<th>Overarching Issues*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge Question ID (if relevant)</td>
<td>Reviewer Agreement with EPA*</td>
</tr>
<tr>
<td>Verbatim Charge Question (if relevant)</td>
<td>Assessment Team Response/Level of Effort*</td>
</tr>
<tr>
<td>Reviewer</td>
<td>Revisions to Toxicological Review</td>
</tr>
<tr>
<td>Topic*</td>
<td>Response to Comment Appendix Location (Pg # and Charge Question)</td>
</tr>
<tr>
<td>Stage at which Comment was Received*</td>
<td>Official Response to Comment</td>
</tr>
<tr>
<td>Verbatim Reviewer Comment</td>
<td>Individual Addressing Comment</td>
</tr>
<tr>
<td>Summary of Reviewer Points/Recommendations</td>
<td>Completion Date</td>
</tr>
<tr>
<td>Major Comment*</td>
<td>Type of Review*</td>
</tr>
</tbody>
</table>

2/22/2013
Appendix E: Scoping

• Primary goal is to understand needs of clients in EPA program and regional offices

• Questions focus on “what” rather than “how” of developing assessment

• Scoping process is an evolving tool
  • Procedures will change as IRIS develops institutional experience and knowledge
  • Meetings may be face-to-face, email, or virtual consultation depending on chemical
Appendix F: Draft Handbook

• Provides information to IRIS teams regarding internal processes and evaluation steps used to develop an assessment.

• Is a work in progress—some components missing (integrating across evidence, conducting dose-response analysis, extrapolation to lower doses and response levels, considering susceptible populations and lifestages, developing candidate values, characterizing confidence and uncertainty, selecting final values)
Appendix F: Draft Handbook

• Discusses literature search and screening:
  • Selecting databases
  • Selecting search terms
  • Augmenting database search
  • Documenting the search
  • Updating the search

• Discusses screening for relevance
  • Review process for excluding; keeping as additional, non primary data source; possible further review; move to full text screening
  • Collation/Sorting
Keywords identified for screening (see below) to identify those appropriate for “snowball”

“Snowball”: Citations added from 2 relevant reviews: 108 unique citations via export using Web of Science

Unpublished studies conducted by Japanese Petroleum Energy Center

Studies moved to Study Quality Evaluation step (“Considered” studies) Conducted January, 2013
Appendix F: Draft Handbook

• Evaluation and Display: Study Quality Evaluation
  • Evaluate before developing evidence tables
  • Use focused questions applied systematically to all primary data
  • Evaluation is endpoint-specific
• Discusses logistics:
  • use two independent reviewers, have procedures for disagreement resolution
  • look for errata, supplemental information
  • correspondence (letters to the editor, editorials) may provide additional background information
• Quality evaluation should be independent of considerations of magnitude and direction of results
Appendix F: Draft Handbook

• Evaluation of Observational Epidemiology Studies
  • Akin to detective work: need to investigate features related to exposure: reliability, validity, probability and level of exposure; outcome and confounders
  • Study characteristics to inform evaluation are in Table F-6 (no mention of confounders)
  • Example worksheet in Figure F-3
Appendix F: Draft Handbook

• Evaluation of Animal Toxicology Studies
  • Table F-7 provides list of questions relating to study features. Based on Klimisch
  • Not all questions of equal importance

• Evaluation of Human Controlled-Exposure Studies
  • Table F-7 is also relevant here
Appendix F: Draft Handbook

• Documenting Study Quality Evaluations
  • Use of tables
  • Gray shading for limitations
  • Goal not to eliminate studies but to understand potential limitations that would affect interpretation
  • ‘Tiering’ of studies can be useful, judgments should be documented

• Reporting Study Results
  • Evidence tables
    • Templates provided for animal and epi evidence
Evaluating Overall Evidence of Each Effect

- Synthesis of epidemiology data
  - Aspects suggesting causality
  - Evaluation of alternative explanations
- Summary descriptors for epidemiology evidence:
  - Sufficient epidemiologic evidence of an association consistent with causation
  - Suggestive epidemiologic evidence of an association consistent with causation
  - Inadequate epidemiologic evidence to infer a causal association
  - Epidemiological evidence consistent with no association
Appendix F: Draft Handbook

- Evaluating Overall Evidence of Each Effect (TCE)
- Synthesis of Animal Toxicology Evidence
  - Principles and considerations for writing a synthesis: there is no formula but key elements to address are discussed
  - Compares two draft versions of text
  - Mechanistic Considerations in Elucidating Adverse Outcome Pathways
    - To inform biological plausibility
Appendix F: Draft Handbook

Dose-Response Analysis
• Selecting Studies for derivation of toxicity values
• Table F-13 shows attributes used to evaluate studies
• Considerations for Combining Data

Data Management and Quality Control
• To minimize errors, improve transparency
• Automate Tasks, provide access to archives
• Tools:
  • BMDS wizard
  • Dragon
  • Dosimetry tool

Considerations for Selecting Organ/System Specific or Overall Toxicity Value
Part II: Chemical Specific Examples

• Example 1: Literature Search and Screening (ETBE)

• Example 2: Evaluation and Display of Studies (DEP)
  • Shows how shading is used for limitations, shows presentation of information in tables for epidemiological studies.
  • Shows evaluation of animal data
    • ++ approach (for how well criteria are met)

• Example 3: Evidence Tables (DEP)
  • Tables for human and animal effects

• Example 4: Evidence Integration (Formaldehyde, epi data for LHP cancers)
  • Shows how use Hill aspects to evaluate causation
Part II: Chemical Specific Examples

• Example 5: Selecting Studies for Derivation of Toxicity Values (DPP)
  • Shows draft assessment text

• Example 6: Dose-Response Modeling Output (TMB, DINP)
  • Shows draft tables of data and BMD modeling results for non-cancer and cancer approaches

• Example 7: Considerations for Selecting Organ/System-Specific Overall Toxicity Values (BaP)
  • Shows tables and figures of candidate values
  • Shows draft assessment text for selection and confidence statement (non-cancer only)