SBA Environmental Roundtable
IRIS Program Developments

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Very Recent IRIS Developments

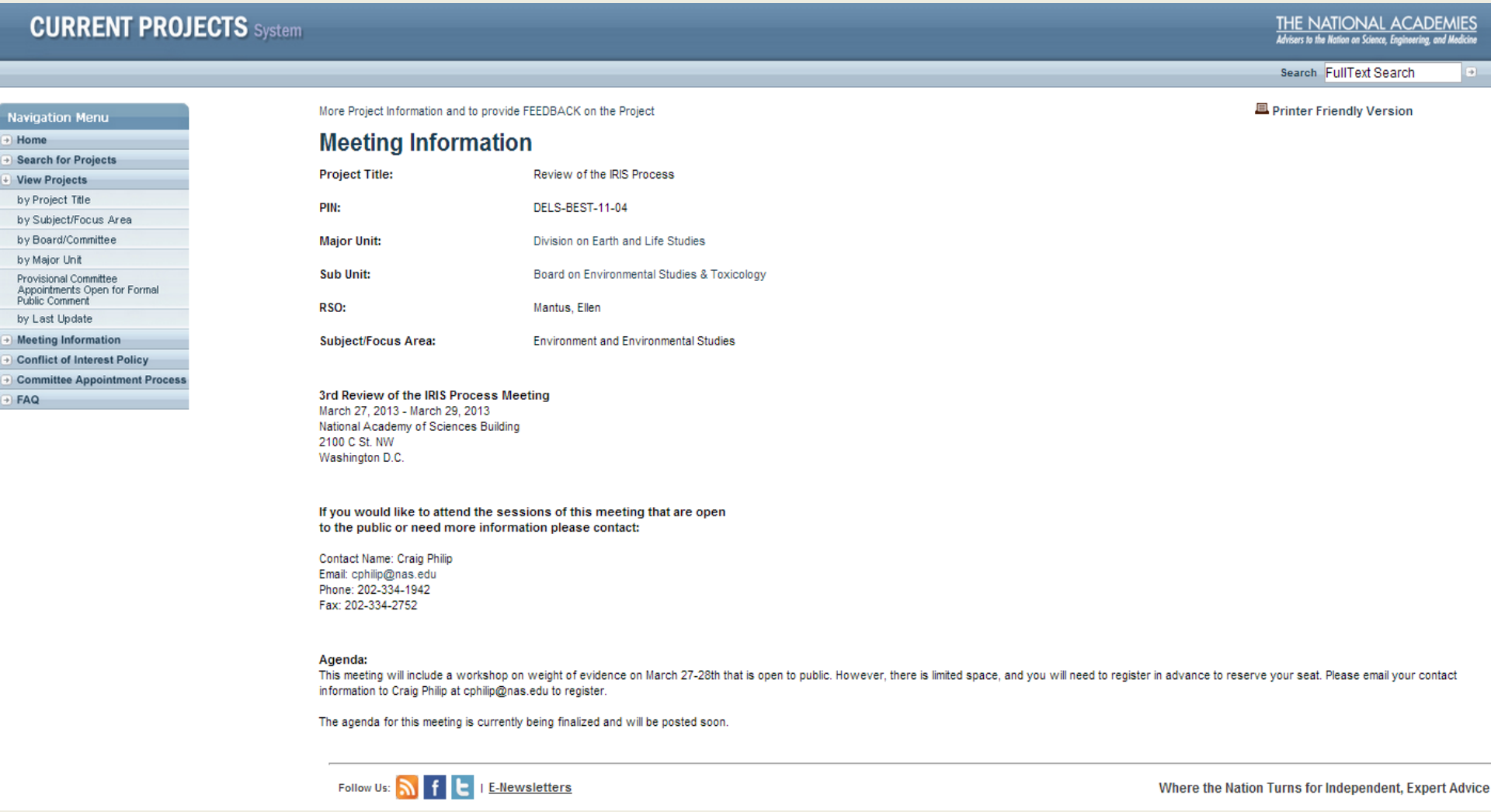
IRIS Program continues to evolve and be a significant focus of attention

- 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



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:

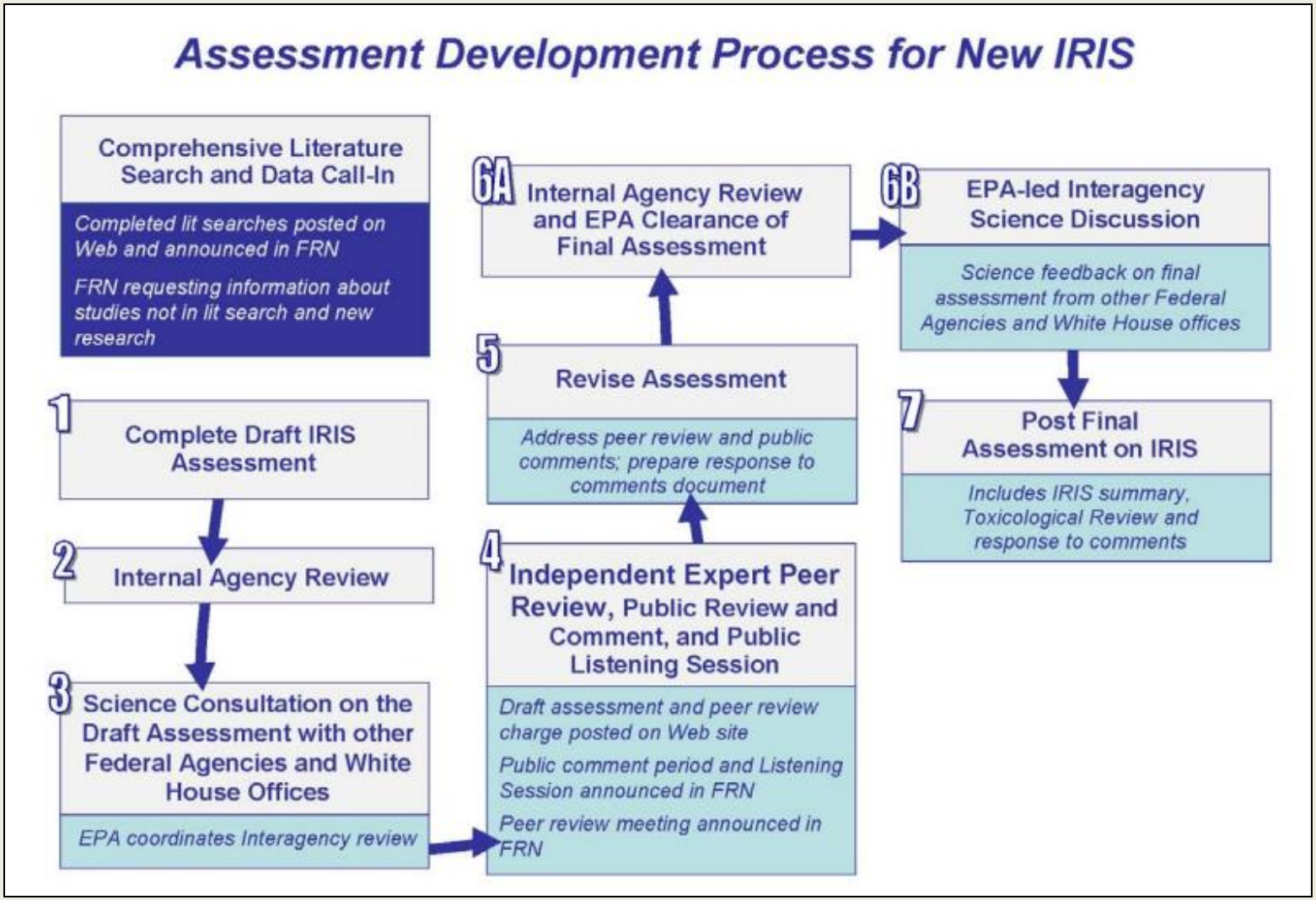
- Stakeholder engagement
- Increased transparency, and
- Using the best available science

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



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

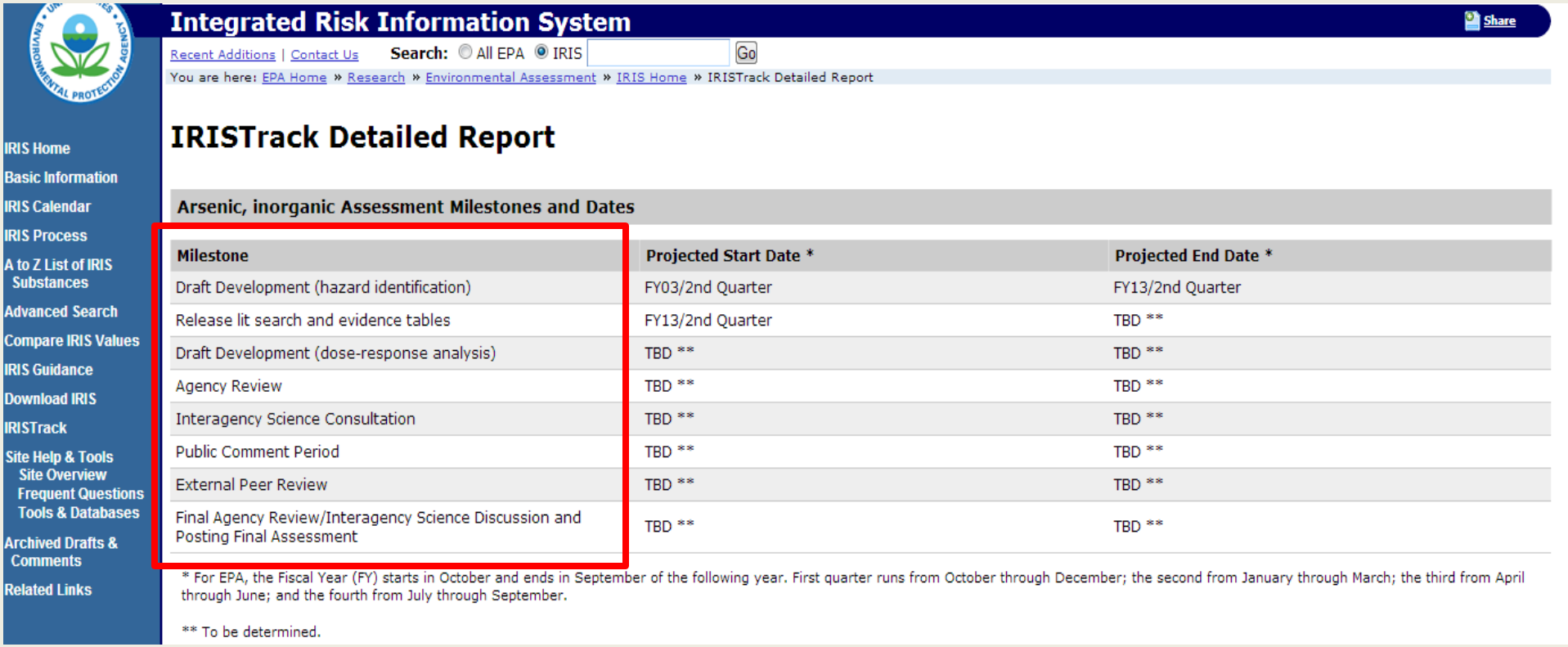
Milestone Changes

- 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

2009 Step	0: Comprehensive Literature Search & Data Call-In		1: Complete Draft IRIS Assessment	2: Internal Agency Review	3: Science Consultation on the Draft Assessment w/Other Federal Agencies & White House Officials	4: Independent Expert Peer Review & Comment; Public Listening Session		6: Internal Agency Review & EPA Clearance of Final Assessment; EPA-Led Interagency Science Discussion	7: Post Final Assessment on IRIS
2013 Mile-stone	Draft Development (Hazard Identification)	Release Lit. Search & Evidence Tables	Draft Development (Dose-Response Analysis)	Agency Review	Interagency Science Consultation	Public Comment Period	External Review	Final Agency Review/Interagency Science Discussion	
	Inorganic arsenic ETBE RDX t-Butanol		Formaldehyde Methanol		Benzo[a]-pyrene Ethylene oxide	Ammonia Trimethyl-benzenes	1,4-Dioxane (inhalation) Biphenyl		

IRISTrack Example: Inorganic Arsenic



Integrated Risk Information System

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Arsenic, inorganic Assessment Milestones and Dates

Milestone	Projected Start Date *	Projected End Date *
Draft Development (hazard identification)	FY03/2nd Quarter	FY13/2nd Quarter
Release lit search and evidence tables	FY13/2nd Quarter	TBD **
Draft Development (dose-response analysis)	TBD **	TBD **
Agency Review	TBD **	TBD **
Interagency Science Consultation	TBD **	TBD **
Public Comment Period	TBD **	TBD **
External Peer Review	TBD **	TBD **
Final Agency Review/Interagency Science Discussion and Posting Final Assessment	TBD **	TBD **

* 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

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

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

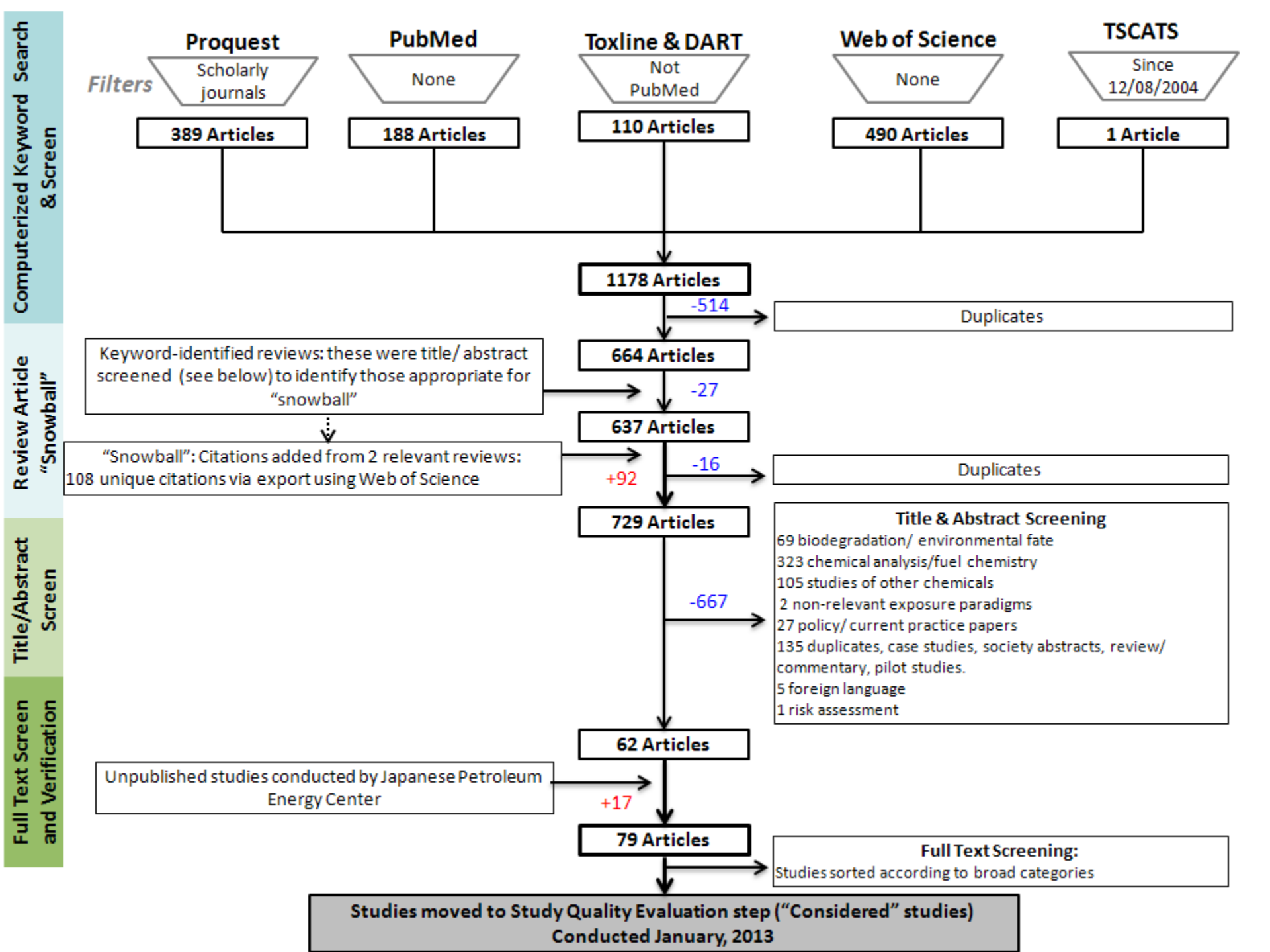
- Provides information to IRIS teams regarding internal processes and evaluation steps used to develop an assessment.

- 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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389 Articles
188 Articles
110 Articles
490 Articles
1 Article
1178 Articles
-514
Duplicates
664 Articles
Keyword-identified reviews: these were title/ abstract screened (see below) to identify those appropriate for "snowball"
-27
637 Articles
"Snowball": Citations added from 2 relevant reviews: 108 unique citations via export using Web of Science
+92
-16
Duplicates
729 Articles
Title & Abstract Screening
69 biodegradation/ environmental fate
323 chemical analysis/fuel chemistry
105 studies of other chemicals
2 non-relevant exposure paradigms
27 policy/ current practice papers
135 duplicates, case studies, society abstracts, review/ commentary, pilot studies.
5 foreign language
1 risk assessment
-667
62 Articles
Unpublished studies conducted by Japanese Petroleum Energy Center
+17
79 Articles
Full Text Screening:
Studies sorted according to broad categories
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

Appendix F: Draft Handbook

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)