

EPA's Integrated Risk Information System

Assessment Development Procedures

Introduction: The Integrated Risk Information System (IRIS) is a U. S. Environmental Protection Agency (EPA) database that contains the Agency's science and science policy positions on chronic human health effects that may result from exposure to environment contaminants. Through IRIS, EPA provides the highest quality science-based human health assessments to support Agency policymaking activities.

Since the 1980s when IRIS began, EPA has taken many steps to improve the IRIS process that make it more accessible and transparent. In addition, the Agency has worked to enhance the independent expert peer review process to assure high quality human health assessments. In its continuing efforts to improve risk assessment practices, EPA has reviewed its development processes for human health assessments that, once completed, are included on IRIS.

The role of other Federal agencies and the public in the IRIS process is to promote communication, sharing of information, and teaming with EPA at key points throughout the nomination and assessment activities. Agencies may identify chemical substances that are critical to their mission and operation, therefore initiating targeted discussions with EPA in the development of risk assessments for these mission critical chemicals. The public is also offered opportunities to bring forth data and expertise to inform the IRIS process. The enhanced transparency brought about by teaming of other Federal agencies and the public with EPA will help identify scientific issues early, which will ultimately help streamline the IRIS process.

I. Annual Chemical Nomination Process

1. EPA Initiates Annual Nomination Process for IRIS Assessments (75 days)

- A. EPA's Office of Research and Development (ORD) issues a *Federal Register* (FR) notice inviting public nominations of chemical substances for ORD to consider for inclusion on the IRIS Program annual agenda (Agenda). Nominations could include chemical substances to consider for the development of new assessments as well as the revision of assessments already on IRIS for which critical new information is available. Nominations must be submitted within 60 days of the solicitation.
- B. Simultaneously, ORD asks the EPA Program and Regional Offices and other agencies to nominate chemical substance(s) for inclusion on the Agenda.
 - a. Agencies include, but are not limited to, HHS, NASA, DOA, DOE, DOT, DOD, OMB, CEQ, and OSTP.
 - b. Each interested agency appoints one point of contact (POC) at the organizational level it deems appropriate. Each agency POC is responsible for keeping their management appropriately informed and for coordinating reviews of draft IRIS documents by that agency.
 - c. ORD appoints the POC in the IRIS program.
 - d. ORD notifies EPA Program and Regional Offices via memorandum to the EPA Deputy Assistant Administrators and Deputy Regional Administrators, with a copy to the intra-Agency IRIS Review Committee (via email), about the request for assessment nominations.

- e. ORD notifies the other agencies via memorandum to the agency POCs (via email) about the request for assessment.
 - f. Other agencies and EPA Program and Regional Offices have 60 days to submit nominations for inclusion on the Agenda; nomination submittals will be considered part of the public record.
 - g. If an other agency or EPA Program and Regional Office does not respond within 60 days of the solicitation ORD will assume that it did not have any nominations for that year.
 - h. Other agencies and EPA Program and Regional Offices provide documentation that supports their interest in the chemical(s) and rationale for consideration to ORD.
- C. At the end of the nomination period, within 15 days, ORD calls a meeting with other agencies and EPA Program and Regional Offices to discuss their nominations, including:
- a. Other agencies' or EPA's Program and Regional Offices' specific questions and concerns about, and recommendations for, adding or updating assessments for the chemical substance(s) that they nominate;
 - b. The importance that other agencies or EPA Program and Regional Offices place on having the chemical substance(s) that they nominate included on the Agenda, and the basis for the nomination; and
 - c. Current or planned research and/or assessments by EPA or the other agencies.

2. EPA Determines Annual IRIS Agenda (30 – 60 days)

- A. ORD applies its published selection criteria to the slate of nominated chemicals.
- B. ORD reviews its available work force and areas of expertise that might be available for new assignments.
- C. ORD prepares the IRIS Program Annual Agenda, which lists the chemical substances for which work will be initiated in the upcoming year, including chemicals selected by ORD and consideration of chemicals nominated in response to **Step 1.A** and **Step 1.B**.
- D. ORD notifies EPA Program and Regional Offices, other agencies, and the public that the IRIS Program Annual Agenda is available.
 - a. Notify EPA Program and Regional Offices by memorandum to the EPA Deputy Assistant Administrators and Deputy Regional Administrators, with a copy to the intra-Agency IRIS Review Committee (via email).
 - b. Notify other agencies by memorandum to agency POCs (via email).
 - c. Notify public by issuing an FR notice announcing the IRIS Program Annual Agenda (new starts and updates).
- E. The other agencies or EPA Program and Regional Offices may decide at this early stage to sponsor or perform research associated with the chemicals selected or proposed to be assessed if they conclude that such work would be beneficial to the assessment or future re-assessments. The results of this research will be considered for inclusion in the IRIS assessment if it is completed within an appropriate time frame as determined by ORD and has undergone independent external peer review (e.g., peer review publications or independent peer review panel evaluations).

- 1 F. The other agencies identify to ORD an initial list of the chemical(s) on the IRIS Program Annual
2 Agenda that they have determined meet the definition of mission critical¹.

3
4 **II. The Assessment Process**

5
6 **1. EPA Conducts Scientific Literature Search (60 – 90 days)**

- 7 A. ORD appoints a chemical manager(s) for each chemical on the IRIS Program Annual Agenda.
8 B. The chemical manager(s) direct an EPA contractor to conduct and complete a comprehensive search
9 of the scientific literature for the chemical.

10
11 **2. EPA Initiates Data Call-In (45 – 60 days)**

- 12 A. After the literature search has been completed for each chemical, ORD publishes an FR notice that
13 notifies the public that completed literature searches for a set of chemicals are available on the IRIS
14 Internet site, and invites the public and other agencies to submit additional scientific information
15 (studies, reports, other assessments, etc.) on the chemical.
- 16 a. FR notice requests information on new research that may be planned, underway, or in press.
 - 17 b. FR notice includes notification that the initial literature review results for each chemical are
18 available on the Internet for review (eliminates submission of information about which EPA
19 is already aware).
 - 20 c. FR notice includes information on how and where to submit scientific information.
 - 21 d. A minimum of 45 days is provided for submission of information.
- 22 B. ORD ensures that EPA Program and Regional Offices and other agencies are aware of the FR notice:
- 23 a. EPA Program and Regional Offices: via email
 - 24 b. Other agencies: via email to agency POCs. Each agency POC is responsible for keeping
25 his/her management appropriately informed.
- 26 C. Other agencies confirm to ORD whether the chemical is mission critical. It is expected that only a
27 few chemicals will receive this designation.
- 28

¹A mission critical chemical is one that is an integral component to the successful and safe conduct of an Agency's mission in any or all phases of its operations. Impacts on use of mission critical chemicals include cessation or degradation of the conduct of the mission and/or unacceptable resource constraints.

1 **3. EPA Begins IRIS Assessment and Develops Draft Qualitative Assessment**
2 **(180 – 240 days)**

- 3 A. ORD identifies and assembles an IRIS assessment team.
- 4 B. ORD reviews new scientific information submitted in response to the call for information in **Step 2**.
- 5 C. ORD assesses the data in the scientific literature and submitted in **Step 2** and develops a draft
6 Qualitative Assessment for the chemical being assessed, including:
- 7 a. summary of potentially important health effects;
- 8 b. summary of information on potential mode(s) of action;
- 9 c. summary of information about potentially susceptible populations;
- 10 d. description of approaches being considered for dose-response assessment including default
11 approaches and types of models under consideration;
- 12 e. identification and discussion of potential uncertainty factors; and
- 13 f. identification of potential uncertainties that impact the qualitative and quantitative aspects of
14 the assessment.
- 15 D. This draft Qualitative Assessment does not include quantification; however, extensive qualitative
16 information including ORD’s interpretation of scientific data and description of potential
17 assumptions and approaches will be included.
- 18 E. The draft Qualitative Assessment completes internal ORD clearance.
- 19 F. The draft Qualitative Assessment completes internal EPA review via the intra-Agency IRIS Review
20 Committee. Intra-Agency comments are deliberative.
- 21

22 **4. EPA Initiates Public and Agency Review of Draft Qualitative Assessment**
23 **(45 – 60 days)**

- 24 A. ORD issues a FR notice inviting the public and other agencies to comment on the draft Qualitative
25 Assessment.
- 26 B. On the publication date of the FR notice, the draft Qualitative Assessment is posted on the IRIS
27 Internet site.
- 28 C. ORD ensures that EPA Program and Regional Offices and other agencies are aware of the FR notice.
- 29 D. The FR notice includes instructions for submitting comments to ORD. The FR notice also requests
30 that the public and other agencies identify missing types of studies and areas where uncertainties
31 might be reduced, modes of action elucidated, or estimation of dose-response informed through new
32 short-term (12 month) research.
- 33 E. Other agencies may identify a chemical as mission critical based on the results of the draft
34 Qualitative Assessment (see Annual Chemical Nomination Process - **Step 2.F**).
- 35 F. All public comments received during the official public comment period must be submitted through
36 E-Gov (www.regulations.gov); all public comments will be part of the official record. Other agency
37 comments are deliberative.
- 38 G. ORD holds a “listening session” during the public review process to allow all interested parties to
39 comment on the draft Qualitative Assessment.

1 **5. EPA Initiates Review of Public and Agency Comments (30 days)**

- 2 A. ORD compiles and reviews all public and other agency comments received on the draft Qualitative
3 Assessment, and shares the comments with EPA Program and Regional Offices and other agencies.
- 4 B. ORD provides other agencies and EPA Program and Regional Offices with information about any
5 significant changes that might occur in the IRIS assessment as a result of the public or other agency
6 comments and listening session.
- 7 C. If another agency or the public wants to discuss with ORD a particular comment or set of
8 comments, they should contact the IRIS POC to arrange a meeting with ORD.
- 9 D. If significant alternative science or science policy judgments are raised by the public, EPA Program
10 or Regional Offices, or other agencies, these will be added to the document and brought forward in
11 the charge to the independent external peer review panel.

12

13 **6. Evaluation of Agency Interest in Closing Data Gaps for Mission Critical**
14 **Chemicals (90 days)**

- 15 A. If another agency is interested in filling a significant data gap, it must first document that the
16 chemical is mission critical (see Annual Chemical Nomination Process - **Step 2.F** and The
17 Assessment Process - **Step 4.E**).
- 18 B. For mission critical chemicals, the agency interested in addressing data gaps will consider the
19 comments provided in **Steps 4 and 5**, and submit to ORD a research plan that documents how the
20 conduct of new research has the potential to reduce uncertainties, clarify the mode-of-action, or
21 inform the estimation of dose-response. The other agency must also show that the proposed research
22 and peer review can be completed in less than 18 months. If desired, a letter of agreement between
23 ORD and the other agency sponsoring the research can be created articulating the relevance of the
24 proposed research to the risk assessment and how the proposed research may inform the risk
25 assessment. Such a letter would indicate the timeframe for expected research to be completed.
- 26 C. The sponsoring agency may decide that an independent 3rd party consultation should be done to
27 evaluate the estimated costs of the proposed research, and the expected benefits of additional
28 research for the assessment. This 3rd party consultation must be completed during this 90 day
29 period.
- 30 D. If a sponsoring agency wants to partner with an external party or any other agency to conduct a
31 study, that decision is theirs to make, but ORD and other interested agencies should be informed.
- 32 E. If no request for developing new short-term research is received, or if no interest in conducting such
33 research is expressed for mission critical chemicals, proceed to **Step 8**.

34

35 **7. Design and Implementation of New Studies for Mission Critical Chemicals**
36 **(365 – 540 Days)**

- 37 A. If in **Step 6** the consequences and interest in closing data gaps are determined to be critical by ORD,
38 in consultation with the intra-Agency IRIS Review Committee and other interested agencies, the
39 agency can sponsor the new research.

- 1 B. ORD will generally allow no more than an 18 month hiatus from the completion of the IRIS
2 assessment to allow for the completion and peer review of studies specified in **Step 6**.
- 3 C. The sponsoring agency develops a detailed research plan and solicits comments and
4 recommendations on the research plan from ORD, in consultation with the intra-Agency IRIS
5 Review Committee, and from other agencies. ORD and the other agencies respond to the sponsoring
6 agency within 30 days, focusing on study design and whether the research, if conducted as planned,
7 is likely to reduce uncertainties (e.g., specific uncertainty factor), clarify the mode-of-action, or
8 inform the estimation of dose-response. The study plan and characterization of potential impacts on
9 the assessment is documented in a letter between the sponsoring agency and ORD, as a complement
10 to the letter discussed in **Step 6.B**.
- 11 D. The agency sponsoring the research will work expeditiously to complete its planning, protocol
12 design, and study implementation. ORD, in consultation with the intra-Agency IRIS Review
13 Committee, will provide timely reviews and responses of any aspect of this work, if requested by the
14 sponsoring agency.
- 15 E. If ORD or the sponsoring agency deems that consultations are warranted, ORD or the sponsoring
16 agency can call meetings and teleconferences to discuss critical issues articulated in correspondence
17 among the agencies. Third-party consultants can be invited by ORD or the other agencies to
18 participate in these meetings and teleconferences.
- 19 F. An agency may also sponsor or perform any other research (that is outside the scope of this effort)
20 associated with the chemical being assessed if it concludes that such work might be beneficial to a
21 future IRIS assessment. Agencies will continue to direct their internal research agendas as they see
22 fit.
- 23 G. The sponsoring agency provides the study report(s) to ORD and other interested agencies
24 immediately upon completion of the study.
- 25 H. Independent External Peer Review (included as part of **Step 7** timeframe):
- 26 a. Upon completion of the study, the sponsoring agency arranges for external peer review of the
27 research report(s) by the scientific community.
- 28 b. The sponsoring agency consults with ORD in determining who will conduct this review, the
29 level of review, and by what means (e.g., panel review).
- 30 c. ORD and the sponsoring Agency provide the studies, peer review comments and disposition
31 of comments report(s) to the public.
- 32 d. If ORD or the sponsoring agency deems that consultation is warranted, ORD or the
33 sponsoring agency may call a meeting to discuss critical issues and significant disagreements
34 about the peer reviews. Third-party consultants may be invited by ORD or the sponsoring
35 agency to participate in this meeting.
- 36 I. ORD, in consultation with the intra-Agency IRIS Review Committee, will consider the results of the
37 new studies carefully as it proceeds with the development of the assessment. Discussion of the new
38 study results will be included in the draft assessment.

40 **8. EPA Completes Draft IRIS Toxicological Review (120 – 270 days)**

- 41 A. ORD completes the draft IRIS Toxicological Review.

- 1 a. The draft IRIS Toxicological Review draws upon the previous draft Qualitative Assessment
2 and the comments received in **Steps 4 and 5**.
- 3 b. ORD reviews and analyzes any new short-term research completed under **Steps 6 and 7**.
- 4 c. The draft IRIS Toxicological Review includes a quantitative assessment, including
5 application of uncertainty factors, mode-of-action information, and dose-response modeling.
- 6 B. The draft IRIS Toxicological Review undergoes internal ORD review (30 – 45 days).
- 7 C. ORD submits the draft IRIS Toxicological Review for internal review via the intra-Agency IRIS
8 Review Committee and addresses intra-Agency comments (30 – 60 days).
- 9 D. Determination of peer review characteristics:
 - 10 a. For mission critical chemicals, ORD will cooperate with other interested agencies to
11 determine the level of peer review (e.g., National Academy of Science (NAS) review, EPA
12 Science Advisory Board (SAB) review, or contractor-led panel peer review), panel
13 disciplines, and the scope of the review.
 - 14 b. For other chemicals, ORD determines the level of peer review, panel disciplines, and the
15 scope of the review.
 - 16 c. ORD develops any contract documentation.

18 **9. EPA Initiates Interagency Review of Draft IRIS Toxicological Review (45 –** 19 **105 days)**

- 20 A. ORD sends the draft IRIS Toxicological Review and draft external peer review charge questions to
21 OMB to initiate interagency review.
- 22 B. ORD develops a charge for interagency reviewers. It is anticipated that the interagency review
23 charge will remain similar for each draft IRIS Toxicological Review, with chemical specific text
24 added as appropriate.
- 25 C. OMB distributes the draft IRIS Toxicological Review, draft external peer review charge questions,
26 and the interagency review charge to interagency reviewers.
 - 27 a. Length of review period is 30 – 60 days and depends on complexity of draft assessment
28 documents.
 - 29 b. OMB facilitates interagency review to help assure timely response within designated
30 review period.
- 31 D. OMB compiles and provides all interagency comments to ORD; other agency comments are
32 deliberative.
 - 33 a. ORD assumes “no comment” from other agencies that do not respond within the designated
34 review period.
 - 35 b. If another agency requests an extension of the review period, both the IRIS POC and OMB
36 POC should be contacted regarding the request and the justification.
- 37 E. ORD addresses the interagency comments and develops a “disposition of comments” document and
38 revises the draft assessment documents, as appropriate, within 15 – 30 days.

- 1 F. Within 15 days after the comment period ends, ORD, OMB, or other interested agencies may call a
2 meeting to discuss and resolve critical issues and significant disagreements articulated in the other
3 agencies' comments on the draft assessment documents.
- 4 a. OMB serves as the facilitator for the meeting.
- 5 b. Areas of disagreement may result in additional charge questions for the external peer
6 review.
- 7

8 **10. EPA Initiates Independent External Peer Review and Releases External** 9 **Draft IRIS Toxicological Review (120 – 280 days²)**

- 10 A. ORD provides the draft IRIS Toxicological Review and peer review charge questions to independent
11 external peer reviewers. Peer reviews are public meetings, generally through a face-to-face meeting
12 of panelists, though some may be held via public teleconference.
- 13 B. Concurrently, ORD publicly releases the draft IRIS Toxicological Review and charge to peer
14 reviewers for public review and comment on the IRIS Internet site.
- 15 a. ORD prepares an FR notice announcing a public comment period of 45 to 60 days.
- 16 b. Length of the public comment period depends on the complexity of the draft IRIS
17 Toxicological Review.
- 18 c. The draft IRIS Toxicological Review and charge to peer reviewers is released on the IRIS
19 Internet site on the day that the FR is published.
- 20 d. Public comment period is open to all stakeholders, including other agencies.
- 21 e. ORD insures that other agencies are aware of the FR notice.
- 22 C. ORD holds a “listening session” during the public comment process to allow all interested parties to
23 comment on the draft IRIS Toxicological Review.
- 24 D. Public comments from Steps B and C are submitted to ORD.
- 25 a. All public comments received during the official public comment period will be submitted
26 through E-Gov (www.regulations.gov); all public comments will be part of the official
27 record.
- 28 b. Comments received by the close of the public comment period will be provided to the
29 external peer review panel at least 30 days in advance of the peer review meeting.
- 30 E. The report of the external peer review panel becomes part of the public record for the IRIS
31 assessment.
- 32

33 **11. EPA Revises IRIS Toxicological Review and Develops IRIS Summary (120** 34 **– 150 days)**

- 35 A. ORD evaluates the external peer review panel report and public comments.
- 36 B. ORD revises the draft IRIS Toxicological Review, as appropriate, and develops the IRIS Summary.
- 37 C. Length of revision process depends on the complexity of the IRIS Toxicological Review and
38 complexity and number of peer reviewer and public comments.

² This time frame does not include reviews conducted by the National Academy of Sciences (NAS).

- 1 D. Within 90 – 120 days, ORD develops a disposition of peer reviewer and public comments and
2 provides the disposition of comments document and the revised IRIS Toxicological Review and
3 IRIS Summary to the external peer review panel members for their comment within 30 days.
- 4 E. ORD provides the disposition of peer reviewer and public comments document and any additional
5 peer review panel comments from **Step 11.D** as an appendix to the IRIS Toxicological Review.
- 6

7 **12. EPA Initiates Final Agency and Interagency Review of the IRIS**
8 **Toxicological Review and IRIS Summary (30 – 45 days)**

- 9 A. ORD sends the final IRIS Toxicological Review and IRIS Summary to OMB for distribution to the
10 other agencies.
- 11 B. In general, this distribution is intended as a final check-in to address any remaining issues and ensure
12 that public and peer reviewer comments were adequately considered or addressed by ORD.
- 13 C. Concurrently, ORD sends the IRIS Toxicological Review and IRIS Summary to the intra-Agency
14 IRIS Review Committee for comment (30 days).
- 15 D. OMB compiles and provides all interagency comments to ORD within 30 days.
- 16 a. ORD assumes “no comment” if the other agencies or EPA Program or Regional Offices do
17 not respond within the designated review period.
- 18 b. If another agency or EPA Program or Regional Office requests an extension of the review
19 period, both the IRIS POC and OMB POC should be contacted regarding the request and the
20 justification.
- 21 E. ORD addresses and resolves any remaining issues in consultation with OMB and other agency or
22 EPA Program or Regional Office POCs within 15 days. Should resolution of any issue not be
23 achieved in discussions with the POC, the other agency or EPA Program or Regional Office that
24 raised the issue may decide to elevate the discussion to their senior management level to achieve
25 resolution. The final decision on IRIS content remains with EPA.
- 26

27 **13. EPA Completion of IRIS Toxicological Review and IRIS Summary (60 days)**

- 28 A. ORD completes the IRIS Toxicological Review and IRIS Summary.
- 29 B. ORD prepares the final assessment to post on the IRIS Internet site.
- 30 C. ORD insures 508 Compliance and EPA web site compliance.
- 31 D. ORD posts the assessment to the IRIS Internet site. ORD completes and maintains the public record.
- 32