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EPA Finalizes its Long-Awaited IRIS Handbook Updating a Number of Key Elements

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On December 22, 2022, EPA's Integrated Risk Information System (IRIS) Program released its *ORD Staff Handbook for Developing IRIS Assessments* (IRIS Handbook). EPA began working on the approaches in the IRIS Handbook after a 2011 National Research Council report recommended several improvements to the overall IRIS assessment process. In 2020, EPA released a draft IRIS Handbook for public comment and commissioned a peer review by the National Research Council.

Established in 1985 to ensure Agency-wide consistent toxicity evaluations, IRIS assessments provide chemical toxicity values for noncancer and cancer human health effects resulting from chronic exposure to chemicals. These values are often utilized in EPA regulations under the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). While chemical risk evaluations conducted under the Toxic Substances Control Act (TSCA) require more information and analysis than that provided by an IRIS assessment, IRIS assessments will likely continue to be used to inform TSCA risk evaluations. State agencies and international bodies also rely on IRIS assessments.

The IRIS Handbook describes important science policy decisions that internal EPA risk assessors will apply when evaluating toxicological information. Although primarily relevant inside EPA, the IRIS Handbook will also be of interest to (1) risk practitioners, (2) state regulators, (3) international regulators, (4) manufacturers and users of chemicals, (5) academics, and (6) environmental groups.

Because of the Handbook's potential for broad impact, external groups should review closely certain aspects of the Handbook, including:

- EPA's detailed approaches and tools for hazard assessment and dose-response, including

the ground rules by which EPA will evaluate, synthesize, and characterize scientific information.

- EPA's roadmaps for: scoping and problem formulation, literature searching and screening, study evaluation, extraction and display of study results, evidence synthesis and integration, derivation of toxicity values, characterizing uncertainty and confidence in toxicity values, and selection of final toxicity values.

- EPA's emphasis on different streams of evidence, including epidemiological and mechanistic information.[1]

The approaches and methods finalized in the IRIS Handbook will impact how EPA develops and characterizes both the human health hazard values for chemicals and the evidence supporting them. For those interested in some of the more detailed aspects of the final IRIS Handbook, below we provide examples of some of the important approaches described in the finalized Handbook.

The IRIS Assessment Development Process: In a significant change from recommendations of the National Research Council in 2014, when developing IRIS assessments, mechanistic information will no longer be treated as a separate stream of evidence on par with animal and human data. As described in the IRIS Handbook,[2] mechanistic information will be treated as a potential modifier in the evidence synthesis step.

Financial Conflicts: When determining who will be selected to conduct peer review of IRIS assessments, EPA will consider financial conflicts that may include significant investments, consulting arrangements, employer affiliation grants or contracts, expert witnesses, consulting arrangements, and honoraria.[3]

Low Confidence Studies: When low confidence studies are identified, the IRIS Handbook states that these studies are given less weight compared to *high* or *medium* confidence results during evidence synthesis and integration,and are generally not used as the primary sources of information for hazard identificationor derivation of toxicity values ***unless*** they are the only studies available.[4]

Consideration of Mechanistic Information: EPA is not taking a one-size-fits-all approach to the consideration of mechanistic information and states that the methods used to synthesize and integrate this evidence will depend on the uncertainties the information helps to address.[5] The Handbook also states that, if the mechanistic evidence is conflicting or insufficient to support an association, this will not change the interpretation of results from the animal and human syntheses.[6]

Expressions of Certainty: For individual health endpoints within an individual evidence stream, evidence will be classified as: *robust*, *moderate*, *slight*, *indeterminate*, or *compelling evidence of no effect*.

When integrating evidence across evidence streams, overall conclusions will be classified as: ***evidence demonstrates***, ***evidence indicates (likely)***, ***evidence suggests***, ***evidence inadequate***, or ***strong evidence supports no effect***. These expressions are visually depicted as:

??? ***Evidence demonstrates***

??? ***Evidence indicates (likely)***

??? ***Evidence suggests***

??? ***Evidence inadequate***

? ? ? ***Strong evidence supports no effect***[7]

Statistical Significance Testing: A *P*-Value of p= 0.05 as a decision point for statistical significance is recognized as "… an arbitrary criterion, with no a priori connection to biological significance." Lack of statistical significance should not automatically be interpreted as evidence of no effect, and not all statistically significant results ("p [8]

Deriving Toxicity Values: Consistent with the EPA Cancer Guidelines, "toxicity values would not be developed for noncancer or cancer hazards with ***evidence suggests*** or suggestive evidence of carcinogenicity conclusions, respectively." However, the Handbook notes that there are some instances where a value might be useful.[9]

Nonlinear Low-Dose Extrapolation: Consistent with past practice, nonlinear low-dose extrapolation is most commonly used for noncancer effects, and the Handbook states that the approach is also "used for cancer effects if there are sufficient data to ascertain the MOA and conclude that it is not linear at low doses, but without enough data to support chemical-specific modeling at low doses."[10]***Uncertainty Factors for Human Variation:*** Citing a technical panel report to EPA, which has not been officially adopted as Agency guidance, the Handbook directs users to reduce the default uncertainty factor (UF) of 10 only in cases where there is dose-response data for the most susceptible population.[11] The Handbook states that the UF "is reduced only if the point of departure is derived or adjusted specifically for susceptible individuals [not for a general population that includes both susceptible and nonsusceptible individuals…]".[12]

FOOTNOTES

[1] For instance, for decades the National Institute of Environmental Health Sciences (NIEHS) has been funding Core Center programs at universities throughout the U.S. Researchers and funders who are interested in having scientific research inform IRIS assessments will want to understand the priorities EPA gives to certain types of scientific information. Academic and industrial sectors have historically spent significant resources on understanding the mechanisms through which chemicals cause their impacts on the human body. While the IRIS Handbook states that "plausibility of an association observed in human or animal studies could be diminished if expected findings are not apparent in mechanistic evidence," it also states that "unexplained inconsistency in the available mechanistic evidence …. will not change the interpretation of the results from the human and animal syntheses (i.e., consideration of biological plausibility will not influence the evidence integration judgment)."

[2] *See* IRIS Handbook at Figure O-1.

[3] *Id.* at 1-4.

[4] *Id.* at 4-5 (emphasis added).

[5] *Id.* at 4-40. For example, the Handbook states that "effort spent on an in-depth analysis of mechanisms associated with a health effect supported by exposure-dependent findings from multiple *medium* and *high* confidence human studies may have relatively little impact on hazard

characterization conclusions." *Id*. at 4-41.

[6] *Id.* at 6-24.

[7] *Id.* at Chapter 6.

[8] *Id.* at 6-19.

[9] *Id.* at 7-1.

[10] *Id.* at 8-11.

[11] We note that, while the Handbook states that it does not supersede existing EPA risk assessment guidelines, the adoption of this 2002 technical panel report as guidance does appear to lead to the adoption of a new approach for the IRIS program.

[12] *Id.* at 8-12.

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