NOTE TO REVIEWERS

History

The draft IRIS assessment of benzo[a]pyrene was released for a 60-day public comment period on August 21, 2013. The comment period was subsequently extended to 90 days, ending on November 21, 2013. In addition, a public meeting was held in December 2013 to provide the public an opportunity to engage in early discussions on the draft assessment and the draft charge to the peer review panel prior to release for external peer review. All public comments provided were taken into consideration in revising the draft assessment prior to posting for external peer review. The complete set of public comments are available on the docket at http://www.regulations.gov (Docket ID No. EPA-HQ-ORD-2011-0391). Appendix G documents EPA's responses to the major scientific issues raised during the public comment period.

Novel aspects of this assessment

Several aspects of the draft IRIS benzo[a]pyrene assessment are novel. The cancer descriptor "carcinogenic to humans" has been chosen, although there are no human studies available where exposure is specifically to benzo[a]pyrene alone because exposure occurs as a component of PAH mixtures. The animal database provides extensive evidence of carcinogenicity in animals and there are multiple human studies indicating carcinogenicity following exposure to PAH mixtures containing benzo[a]pyrene. Although it is likely that multiple carcinogens present in PAH mixtures contribute to the carcinogenic responses, strong evidence is available from several studies of humans exposed to PAH mixtures supporting a contributing role for benzo[a]pyrene DNA adducts in inducing key mutagenic precursor cancer events in target tissues, and there is strong evidence that these key precursor events occur in humans. Additionally, this is the first assessment to develop a slope factor for estimating cancer risk by the dermal route of exposure. Dermal exposure to benzo[a]pyrene is of particular interest because dermal studies indicate point of contact tumor formation. Finally, this assessment includes an analysis of available genomics data to inform the mode of action.

Implementation of NRC recommendations

In April 2011, the National Research Council (NRC) released its *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. In addition to offering comments specifically about EPA's draft formaldehyde assessment, the NRC made several recommendations to EPA for improving the development of IRIS assessments. EPA agreed with the recommendations and is implementing them consistent with the Panel's "Roadmap for Revision," which viewed the full implementation of their recommendations by the IRIS Program as a multi-year process.

In response to the NRC's 2011 recommendations, the IRIS Program has made changes to streamline the assessment development process, improve transparency, and create efficiencies in the Program. The NRC has acknowledged EPA's successes in this area. In May 2014, the NRC released their report *Review of EPA's Integrated Risk Information System Process* reviewing the IRIS assessment development process and found that EPA has made substantial improvements to the IRIS Program in a short amount of time. As part of this review, the committee evaluated the August 2013 public comment draft IRIS assessment of benzo[a]pyrene to gauge EPA's progress in implementing the 2011 NRC recommendations. In their report, the NRC states that "the new document structure, which is reflected in the toxicological review of benzo[a]pyrene, leads to better organized and streamlined assessments and reduces redundancies" and that "the draft assessment shows that the IRIS program has taken several additional steps toward addressing the recommendations in the 2011 NRC formaldehyde report."

The draft benzo[a]pyrene assessment represents a significant advancement in implementing the NRC recommendations. This assessment is streamlined, and uses tables, figures, and appendices to increase transparency and clarity. It is structured to have distinct sections for the literature search/screening strategy and study selection, hazard identification, and dose-response assessment. The assessment includes a comprehensive, systematic, and documented literature search and screening approach, provides the database search strategy in a table (databases, keywords), visually represents the inclusion and exclusion of studies in a flow diagram, and all of the references are integrated within the Health and Environmental Research Online (HERO) database. The evidence is presented in standardized summary and evidence tables, and exposure-response arrays. The hazard identification and dose-response sections include subsections based on organ/system-specific effects in which the evidence is synthesized within datasets for each target organ/system and integrated across all datasets for each target organ/system and across different target organs/systems.

In the draft benzo[a]pyrene assessment, the IRIS Program has attempted to transparently and uniformly identify strengths and limitations that would affect interpretation of results. All animal studies of benzo[a]pyrene involving repeated oral, inhalation, or dermal exposure that were considered to be of acceptable quality, whether yielding positive, negative, or null results, were considered in assessing the evidence for health effects associated with chronic exposure to benzo[a]pyrene. These studies were evaluated for aspects of design, conduct, or reporting that could affect the interpretation of results and the overall contribution to the synthesis of evidence for determination of hazard potential using the study quality considerations outlined in the Preamble. A brief summary of the evaluation is included in the section on methods for identifying and selecting studies. Information on study features related to this evaluation is reported in evidence tables and documented in the synthesis of evidence. Discussion of study strengths and limitations (that ultimately supported preferences for the studies and data relied upon) were included in the text where relevant.

In this assessment, the IRIS Program is using existing guidelines to systematically approach the integration of noncancer human, animal, and mechanistic evidence. In conducting this analysis and developing the synthesis, the IRIS Program evaluates the data for the: strength of the relationship between the exposure and response and the presence of a dose-response relationship; specificity of the response to chemical exposure and whether the exposure precedes the effect; consistency of the association between the chemical exposure and response; and biological plausibility of the response or effect and its relevance to humans. The IRIS Program uses this weight of evidence approach to identify the potential hazards associated with chemical exposure.

The IRIS benzo[a]pyrene assessment provides a streamlined presentation of information, integrated hazard identification of all toxic effects, and the presentation of organ/system-specific reference values. Additionally, consistent with the goal that assessments should provide a scientifically sound and transparent evaluation of the relevant scientific literature and presentation of the analyses performed, this assessment contains an expanded discussion on the rationales for study evaluation and selection, as well as other key assessment decisions. Appendix F of the draft assessment documents where the recommendations from Chapter 7 of the NRC 2011 report have been implemented in this assessment.