



November 21, 2013

Office of Environmental Information (OEI) Docket  
Mail Code: 28221T  
U.S. Environmental Protection Agency  
1200 Pennsylvania Ave., NW.  
Washington, DC 20460

Submitted via <http://www.regulations.gov>

**Re: Comments on the IRIS Toxicological Review of Benzo[a]pyrene (Public Comment External Review Draft), Docket ID No. EPA- HQ-ORD-2011-0391**

Dear Sir or Madam:

In an August 2013 Federal Register Notice, EPA announced the release of the Integrated Risk Information System (IRIS) draft toxicological review of benzo[a]pyrene (herein referred to as “draft BaP assessment”).<sup>1</sup> Subsequently, in October 2013, EPA also announced an extension of the comment period and inclusion of benzo[a]pyrene (BaP) to the agenda for the December 2013 IRIS bimonthly meeting.<sup>2</sup> The draft BaP assessment includes an oral reference dose, inhalation reference concentration, oral slope factor, inhalation unit risk, and a dermal slope factor. The previous 1987 assessment only assessed potential cancer risks.

The American Chemistry Council<sup>3</sup> and its Center for Advancing Risk Assessment Science and Policy (ARASP)<sup>4</sup> are committed to reviewing draft IRIS assessments to ensure that they benefit from the National Research Council (NRC) recommendations for improving the IRIS program<sup>5</sup>

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<sup>1</sup>78 Fed. Reg. 51719 (.). 78 Fed. Reg. 51719 (Aug. 21, 2013).

<sup>2</sup>78 Fed. Reg. 63464 (.). 78 Fed. Reg. 63464 (Oct. 24, 2013).

<sup>3</sup> The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing.

<sup>4</sup> ARASP is a coalition, managed by the ACC, of 19 organizations focused on promoting the development and application of up-to-date, scientifically sound methods for conducting chemical assessments. ARASP members include: Acrylonitrile Group, ACC's Chlorine Chemistry Division, Ethylene Oxide Panel, Formaldehyde Panel, Hexavalent Chromium Panel, High Phthalates Panel, Hydrocarbon Solvents Panel, Olefins Panel, Oxo Process Panel, Propylene Oxide/Propylene Glycol Panel, Public Health and Science Policy Team, Silicones Environmental, Health and Safety Center of North America and Vinyl Chloride Health Committee, American Cleaning Institute, American Petroleum Institute, CropLife America, Halogenated Solvents Industry Alliance, Nickel Producers Environmental Research Association and Styrene Information and Research Center.

<sup>5</sup> National Research Council, Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011), Chapter 7. Available at: [https://download.nap.edu/catalog.php?record\\_id=13142](https://download.nap.edu/catalog.php?record_id=13142)



and EPA's IRIS program enhancements.<sup>6</sup> ARASP's review includes ensuring that current and future IRIS assessments employ a transparent systematic review process and utilize the best available science, data and methodologies. Unfortunately, except for the inclusion of new evidence tables and the relocation of some supporting information to the appendices, the draft BaP assessment represents only minimal changes to implement a more scientifically defensible IRIS evaluation approach.

We offer the following comments and recommendations to assist EPA in improving the assessment.

#### 1) Implementation of the NRC IRIS Recommendations

It has been 31 months since the NRC highlighted recurring problems with EPA IRIS assessments and issued broad sweeping recommendations to improve the program. Although IRIS assessments now rely more on tables, figures, and appendices to present information than in the past, EPA has yet to fully implement all of the NRC recommendations. In the draft BaP assessment, Appendix F, EPA describes its implementation of the NRC recommendations and declares that many recommendations have been implemented or partially implemented. As delineated below, however the assessment falls short of meeting the NRC recommendations.

##### A. Data Quality

In the draft BaP assessment, the various studies described in tables and figures are presented as being of equal quality. However, all the studies are not of equal quality and this type of presentation belies a weight of evidence approach to evaluate and integrate information based upon its quality. While the Preamble mentions some general quality characteristics and states, at page xiv, that at Step 1 EPA "applies consistent criteria to evaluate study quality" and at page 2-1 that studies "were evaluated using general study quality characteristics," there is no explanation of how EPA systematically evaluated all the studies for their quality. Information pertaining to the quality of the individual studies is missing from all the tables/figures and from the discussion of the non-cancer endpoints in the Hazard Identification section. EPA did separate human evidence into tiers for the cancer evaluation based on the quality of the exposure analysis and other unspecified study design features, but EPA did not conduct a similar exercise for the available animal data when evaluating potential non-cancer or cancer effects.

Also, in the draft BaP assessment, as with many previous IRIS assessments, EPA appears to have chosen studies with the lowest point of departure as the critical effect for each endpoint of concern. We recommend that the figures in Chapter 1, the Hazard Identification section, clearly identify whether EPA considers the study to be

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<sup>6</sup> July 2013, EPA announced enhancements to IRIS assessment process; <http://www.epa.gov/iris/process.htm>



of high, medium or low quality. EPA should clearly identify study quality characteristics and describe how each of the studies meets, or does not meet, these criteria. For animal data, such criteria could include a clear evaluation of study design, sample size, statistical power, and the dose-response and exposure characterization. Similarly, Section 1.2.1, the Weight of Evidence Evaluation for Non-Cancer Effects, should include a discussion of the quality of the chosen studies.

## B. Evidence Tables

The evidence tables only appear to provide selected information from each study. For example, where a study evaluated effects at multiple days, only a few select dates are presented and the time points presented appear to be those days when effects were seen. We recommend presenting all the data, positive and negative, equally within the evidence table. Without an equal and transparent presentation of all the data, a synthesis of the information could be skewed.

## C. Systematic Review

In conducting a systematic review, EPA needs to develop a clear and transparent process for evaluating and synthesizing evidence. In the draft BaP assessment, EPA relied on Chen et al. (2012) for the critical effect for the Reference Dose (RfD). While table ES-1 refers to the effect as being developmental toxicity, further analysis of the study identifies the critical effect as a decrease in anxiety-like behavior in rats and mice. Unfortunately, while the draft BaP assessment does note that studies have examined anxiety, attention, and hyperactivity in children and the association with BaP adducts, the assessment does not integrate all the information and explain why a decrease in anxiety, as measured in animal models, should be considered an adverse effect. Instead of fully describing why this endpoint is appropriate, EPA in summary tables, such as ES-1, refers to this decreased anxiety as “neurobehavioral changes” and “developmental toxicity.”

For the reasons mentioned above and in response to the general charge question # 3 for peer reviewers<sup>7</sup>, the draft BaP assessment does not demonstrate successful implementation of the NRC recommendations related to thoroughly evaluating critical studies with standardized approaches that are clearly formulated. Nor does the draft assessment provide a “strengthened, more integrative, and more transparent discussion of weight of evidence.”

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<sup>7</sup> NCEA Proposed Draft Charge to the Science Advisory Board for the IRIS Toxicological Review of Benzo[a]pyrene (August 2013). General Charge Question #3: NRC (2011) states that “all critical studies need to be thoroughly evaluated with standardized approaches that are clearly formulated” and that “strengthened, more integrative, and more transparent discussions of weight of evidence are needed.” NRC also indicated that the changes suggested would involve a multiyear process. Please comment on EPA’s success thus far in implementing these recommendations.



We strongly recommend that EPA revise the draft BaP assessment as described above. As well, EPA should publicly articulate a realistic timeline for completing and fully implementing all of the NRC recommendations. EPA should identify any new guidance documents, handbooks or procedures it has implemented in support of the NRC recommendations. For those documents under development, EPA should provide a clear timeline for completion including opportunities for public comment.

## 2) Discussion of Problem Formulation and the Causal Question Being Addressed

The draft BaP assessment should include an explanation of EPA's problem formulation for BaP. Currently, a few sections throughout the assessment highlight some elements of problem formulation (e.g. "Scope of IRIS Program" on page xiv and "Occurrence and Health Effects" on page xxxii) but these sections do not adequately address problem formulation. In particular, since EPA notes that BaP is universally present in mixtures, EPA should discuss the relevance and utility of an IRIS assessment that evaluates BaP in isolation. We recommend including a separate section on the importance of undertaking a review of BaP, the goals and scope of a BaP assessment and the general potential areas of concern for human health associated with relevant BaP exposure levels.

## 3) Inclusion and Review of All Available Relevant Data

The draft BaP assessment includes a discussion of the literature search strategy and study selection process. This section of the document includes information on the search strategy used to identify health effect studies, search outcomes, and selection of studies for hazard identification. EPA notes that the literature for BaP is extensive and that all animal studies involving oral, inhalation or dermal exposure to BaP were considered. However, the draft BaP assessment does not appear to include all available and relevant dermal studies. For example, Roelofzen et al. (2010)<sup>8</sup> evaluated patients that received coal tar treatments for psoriasis and eczema and found no statistically significant increase in overall cancer, skin cancer, internal cancer, or cancer of specific sites. Specifically, EPA should ensure that all available study data (e.g., studies involving exposure to BaP via the use of coal tar pharmaceuticals) are reviewed and considered in the weight of evidence determination for adverse health effects.

## 4) Utility of the Preamble

General charge question 1 asks the peer reviewers to "comment on whether the new Preamble provides a clear and concise description of the guidance and methods that EPA uses in developing IRIS assessments." We continue to find the Preamble insufficient.

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<sup>8</sup> Roelofzen, J., K. Aben, U. Oldenhof, P. Coenraads, H. Alkemade, P. van de Kerkhof, P. van der Valk, and L. Kiemeny. 2010. No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. *Journal of Investigative Dermatology* 130: 953.



The Preamble, for example, fails to provide a clear description of specific search strategies, exclusion and inclusion criteria (including specific criteria by which study quality was judged), and weight of evidence approaches as the NRC recommended. Instead, it provides an abbreviated view of EPA policies, guidance documents and standard practices, and not the detail necessary to provide useful information on how the Agency reviews or weighs the scientific information for inclusion in the BaP assessment.

Section 3.1 of the Preamble discusses assessments of chemical mixtures. The draft BaP assessment, however, does not provide an assessment of mixtures. Similarly, section 5.2 of the Preamble discusses standardized descriptors an assessment *may* use to characterize epidemiological evidence, but which are not applied in the draft BaP assessment. In providing this abbreviated view, the Preamble omits critical information and may lead readers to incorrectly interpret EPA guidance. In addition, many of complexities of the EPA guidance documents are oversimplified in the current Preamble.

5) Adequate Peer Review of New Methods

The draft BaP assessment includes derivation of the IRIS Program's first dermal slope factor. EPA has not formally established a methodology for extrapolating dermal toxicity from animals to humans but several approaches for consideration are presented in the draft BaP assessment. Since this new methodology has yet to be peer reviewed, we strongly recommend that the external review panel include sufficient expertise in dermal dosimetry to adequately comment on the ability of the available BaP studies to be predictive of relevant exposure dermal scenarios.

6) Additional Suggested Charge Questions:

In addition to the current charge, the final BaP assessment would likely be strengthened if EPA includes explicit questions for peer reviewers on the following topics:

A. Inclusion of Forestomach Tumors.

While this information is lacking from Tables 2-8 and 2-10, the summaries of uncertainties, EPA does acknowledge that the rodent forestomach may be quantitatively more sensitive compared to oral or esophageal tumors in humans. However, based on the cancer analysis, it is the forestomach tumors that drive the cancer risk values. If these tumors were removed from the analysis, the risk values would change significantly. While the EPA Cancer Guidelines do state that "site concordance is not always assumed between animals and humans," they also state (at page 2-22) that "site concordance of tumor effects between animals and humans should be considered in each case." We recommend that EPA more fully consider concordance of the forestomach tumors. Also, the charge to the peer reviewers should specifically seek comment on their inclusion.



B. Confidence in the RfC and RfD values

The evaluation of confidence in the reference values should be further explained and justified. EPA has assigned the reference concentration (RfC) as having low-medium confidence. However, the Archibong et al. (2002) study was not sufficiently robust to allow for the determination of a no observed adverse effect level, thus it is not clear why the study was considered adequate for use in the draft BaP assessment. Due to the weaknesses in this study, as well as the overall database, uncertainty factors of 3000 were applied. As this is the maximum value EPA would generally apply when quantifying an RfC, it is not clear how EPA can state that this overall RfC determination has low-to-medium confidence. Peer reviewers should be asked to explicitly comment on the RfC confidence rating. Similarly, considering that the critical effect for the reference dose (RfD) is a decrease in anxiety, peer reviewers should be asked to explicitly comment on EPA's determination that the confidence in the RfD is medium.

Please feel free to contact either one of us by email ([Nancy\\_Beck@americanchemistry.com](mailto:Nancy_Beck@americanchemistry.com) or [Kimberly\\_Wise@americanchemistry.com](mailto:Kimberly_Wise@americanchemistry.com)) or phone (202-249-7000) with any questions.

Regards,



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