

Chris Gennings: Preliminary comments
Review of EPA's Charge Questions:

3a. Oral reference dose for effects other than cancer (section 2.1). *The draft assessment proposes an overall reference dose of 3×10^{-4} mg/kg-d based on developmental toxicity during a critical window of development. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, and applying uncertainty factors? Does the discussion of exposure scenarios (section 2.1.5) reflect scientific considerations that are implicit for exposures during a critical window of development?*

RESPONSE: The draft assessment does not adequately address the critical window of development. For example, the developmental toxicity studies described on page 2-2 (lines 9-10) describe oral exposures during "gestational or early postnatal development". However, whether the studies include the critical window of development is not discussed. Similarly in the reproductive toxicity section (page 2-4) and immunotoxicity section (page 2-5), statistically significant dose-response relationships were observed in sub-chronic reproductive toxicity studies of both male and female mice; the sex of the immunotoxicity studies is not described. Seemingly, with a dose-response effect the dose range and timing of exposure were appropriate to see an effect. However, the potential impact of early-life exposure and later life effects may exacerbate these effects; this was not addressed.

The discussion of the selected studies is otherwise adequate; this reviewer is not aware of other important studies that should be included. The discussion around the calculation of PODs and uncertainty factors is thorough and adequate.

As the document states, "uncertainty exists due to concurrent exposure to other PAHs and other components of the mixture (such as metals)." (page 2-1, lines 29-30) However, this issue is not further addressed in considerations of exposure scenarios and the potential increase in risk due to cumulative exposure to mixtures of PAHs. This is an important omission to this section.

3c. Oral slope factor for cancer (section 2.3). *The draft assessment proposes an oral slope factor of 1 mg/kg-d based on alimentary tract tumors in mice. Is this value scientifically supported, giving consideration to the intermediate steps of selecting studies appropriate for dose-response analysis and calculating points of departure?*

RESPONSE: The relevance of oral exposure studies in rodents is not adequately described. That is, why 2-year oral bioassay studies are relevant to human exposure should be described.

The description of the selection of studies appropriate for dose-response analysis for calculating PODs is reasonable and seemingly adequate. The description of uncertainty factors is appropriate. The summary tables are helpful for the reviewer.

The document states “that the oral slope factor should only be used with lifetime human exposures <0.1 mg/kg-day, because above this level, the dose-response relationship is not expected to be proportional to benzo[a]pyrene exposure.” (page 2-30, lines 23-25). The relevance of this assumption of human exposure should be further discussed, especially in consideration that the exposure is actually to mixtures of PAHs.

3d. Inhalation unit risk for cancer (section 2.4). *The draft assessment proposed an inhalation unit risk of 0.5 per mg/m³ based on a combination of several types of benign and malignant tumors in hamsters. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis and calculating points of departure?*

RESPONSE: The assumptions used to derive the unit risk (that “any metabolism of benzo[a]pyrene is directly proportional to breathing rate and that the deposition rate is equal between species”; page 2-35, lines 6-8) should be evaluated. Is this a reasonable assumption

The low-exposure extrapolation from the BMCL₁₀ in the multi-stage Weibull model used to derive the inhalation unit risk is reasonable. Appendix E provides further details. Again, the document should address how reasonable it is that lifetime human exposures will be <0.3 mg/m³ (i.e., human equivalent POD). Otherwise, the dose-response relationship is not expected to be proportional to benzo[a]pyrene exposure.

3e. Dermal slope factor for cancer (section 2.5). *The draft assessment proposes a dermal slope factor of 0.006 per ug/day based on skin tumors in mice. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, and scaling from mice to humans? Does the method for cross-species scaling (section 2.5.4 and appendix E) reflect the appropriate scientific considerations?*

RESPONSE: The discussion of study selection seems adequate and reasonable. The calculations of the PODs and methods for scaling from mice to humans seem reasonable.

4. Executive summary. *Does the executive summary clearly and appropriately present the major conclusions of the assessment?*

RESPONSE: The primary missing part of the document is the explanation for the assessment of benzo[a]pyrene alone and not in a cumulative assessment of PAH mixtures. Presumably, benzo[a]pyrene may serve as the index chemical in a cumulative risk assessment of PAH mixtures. This should be stated. There are several places where the mixtures are described in regards to human exposure, but no clear explanation of the role of benzo[a]pyrene in the evaluation of PAH mixtures. For example, in a PAH mixture are the RfDs and RfCs of a single component adequate? This explanation should be included in the Executive Summary to set the stage for the focus on only benzo[a]pyrene in the document.

The multiple sources of exposure are described in the gray box on page 1 – however, it is not clear if there truly is a dominant source of exposure or does it really depend on human behavior.

The literature suggests that benzo[a]pyrene is an endocrine disruptor. With the description of its potential effect on birth weight, postnatal body weight and fertility it might follow. There are so many other endocrine disruptors that humans are commonly exposed to. This should be addressed. Is the effect different across sex? Should there be reference values that are sex dependent?

Several places in the ES (e.g., page xxxvii, lines 11-13) the statement is made that “confidence in the RfC is bolstered by consistent effects observed by ... similar effects observed in human populations exposed to PAH mixtures.” What does this mean? Does it imply that benzo[a]pyrene is the only active component in the PAH mixture? Does it mean the effect level is similar between the single chemical exposure in rodents to the mixture in humans, or just that there is a similar type of effect?

The document should address more directly the potential impact of early life susceptibility on later life risk of cancer and other diseases. It is mentioned on page xxxix (lines 27-29) but not adequately developed. Is there evidence of the potential degree of increased risk due to early life exposure? How relevant are the animal models used in this assessment to this issue? The use of ADAFs of 10-3-fold adjustments is stated – but is the evidence sound about this level of adjustment?