Informal Comments of the National Institute for Occupational Safety and Health on the June 2012 Interagency Science Consultation draft
Toxicological Review of Benzo[a]pyrene
July 10, 2012

The National Institute for Occupational Safety and Health (NIOSH) thanks the U.S. Environmental Protection Agency (EPA) for the opportunity to comment on the June 2012 Interagency Science Consultation draft ***Toxicological Review of Benzo[a]pyrene*** and June 2012 ***EPA Proposed Draft Charge to the Science Advisory Board for the IRIS Toxicological Review of Benzo[a]pyrene*** prepared in support of summary information on the Integrated Risk Information System (IRIS).

Human chemical carcinogenesis is a complex process and rarely does a single chemical exposure occur (as noted in the draft document.) Benzo[a]pyrene (BaP) has been known for many years as a complete carcinogen in the mouse skin model. The presented weight of evidence supports a carcinogenic mechanism in humans that involves metabolic activation and ultimately gene mutation.

1.a) NIOSH recommends that the discussion of human interindividual variation be expanded. Although it is mentioned in relation to CYP1A1 variation, there are many more studies than those cited and little agreement among them. In addition, gene induction varies considerably. For example, NIOSH authors reported a 26.6—100 fold variation in induction of CYP1A1 by BaP and a 12.4—40 fold variation in CYP1B1 induction among 20 different human samples [Keshava et al. 2005; John et al. 2010].

b) The statement "…there is strong evidence that the key precursor events of benzo[a]pyrene's mode of action are likely to be associated with tumor formation in humans" is somewhat overstated (p. 1-72). Tobacco smoke is a carcinogen and a complex chemical mixture. The principal target tissue in humans is the lung, so when lung tumors are examined for "key precursor events" (pp. 1-70—1-72), a wide variety of biomarkers are found and some resemble those expected from pure BaP exposure.

c) The issue of DNA repair capability needs to be considered carefully and expanded (one paragraph on these issues appears on page 1-68.)

Given the observations above concerning interindividual variation (in carcinogen metabolism, activation, detoxification and DNA repair), it seems imperfect for a carcinogen like BaP, which always appears in nature as a component of a complex mixture, to attach a "Reference Dose" (POD) for humans.

2. NIOSH has some concern about the method selected for interspecies scaling of dermal cancer risks. The Knafla et al. [2011] study cited by EPA concluded that the interspecies scaling method EPA is using for dermal carcinogenicity, scaling according to body weight$^{3/4}$, was not applicable to interspecies scaling of dermal cancer risks. NIOSH notes that EPA has stated appropriately that "An established methodology does not exist to adjust for interspecies differences in dermal toxicity at the point of contact" (p. 2-39, Table 2-12). Furthermore, EPA included the choice of body weight$^{3/4}$ for interspecies scaling of the dermal slope factor as a charge question for peer reviewers (question 3 under "Dermal Slope Factor" on p. 5 of the draft charge to reviewers). NIOSH believes the question of interspecies scaling for dermal cancer risk is an important one, and supports EPA in raising this issue as a charge question to the peer reviewers.

Typographical error noted in Supplemental information, page B-3 title and in Table of contents, p. iii: "reponse"

References (.pdfs can be provided)

John K, Divi RL, Keshava C, Orozco CC, Schockley ME, Richardson DL, Poirier MC, Nath J, Weston A [2010]. *CYP1A1* and *CYP1B1* gene expression and DNA adduct formation in normal human mammary epithelial cells exposed to benzo[a]pyrene in the absence or presence of chlorophyllin. Cancer Lett 292(2):254-260.

Keshava C, Divi RL, Whipkey DL, Frye BL, McCanlies E, Kuo M, Poirier MC, Weston A [2005]. Induction of *CYP1A1* and *CYP1B1* and formation of carcinogen–DNA adducts in normal human mammary epithelial cells treated with benzo[a]pyrene. Cancer Lett 221(2):213-224.