**Informal Comments of the National Institute for Occupational Safety and Health on the June 2011 Interagency Science Consultation draft**
***Toxicological Review of Benzo[a]pyrene***
**July 1, 2011**

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 2011 Interagency Science Consultation draft ***Toxicological Review of Benzo[a]pyrene*** and the ***Draft Charge to External Reviewers for the IRIS Toxicological Review of Benzo[a]pyrene*** prepared in support of summary information on the Integrated Risk Information System (IRIS). The following comments are intended to assist EPA in assessing hazards from benzo[a]pyrene.

***Major comments about the overall document:***

1. This risk assessment expands considerably on the earlier IRIS risk assessment for BaP by adding a non-cancer RfD and RfC, and by adding cancer slope factors for inhalation and dermal exposures. For the most part, these are straightforward applications of established risk assessment methods, and do not raise new methodological issues.

The proposed dermal slope factor for BaP-induced skin tumors does break new ground, as the first dermal slope factor to be developed in the IRIS program. NIOSH notes that methods for extrapolating from dermal exposures in experimental animals to human risk estimates for skin cancer are not well-developed. EPA has clearly recognized this by exploring several possible methods of extrapolation for dermal exposures in Appendix H, and by including a question on these methods in the charge questions for peer reviewers. NIOSH commends EPA for raising this issue, and notes that dermal exposures are of substantial concern in the occupational setting.

Several possible alternative methods of animal-to-human extrapolation of dermal exposures are presented in Appendix H: 1) No interspecies adjustment to daily applied dose (POD) in mouse model; 2) Cross-species adjustment based on whole body surface-area scaling; 3) Cross-species adjustment based on body weight; and 4) Cross-species adjustment based on allometric scaling using body weight to the 3/4 power. The potential impact of the choice of interspecies scaling methods is explored in Table H-1 and appears to cover a 2500-fold range of estimated risks for a given exposure. Therefore, the choice of the interspecies scaling method has a substantial impact on the estimated risk to humans.

NIOSH notes that three of the four alternative interspecies scaling factors discussed in Appendix H – specifically approaches 2, 3, and 4 – are those which have been customarily applied for interspecies scaling of systemic carcinogens; i.e., carcinogens that are systemically absorbed and that produce tumors at sites distal to the site of contact. It is not obvious why approaches 2, 3, or 4 should be applicable to estimating risks from a site of contact carcinogen, such as dermally-applied BaP. No rationale, either theoretical or empirical, is given in Appendix H for assuming that dermal carcinogenicity should scale according to any of the proposed dose metrics.

NIOSH considers that an interspecies scaling factor for dermal exposures should be based on the generally accepted principles of interspecies dose equivalency. The derivation of the

interspecies scaling factors for systemic carcinogens, such as allometric scaling using body weight to the 3/4 power, starts with the premise that an equal concentration of the proximate carcinogen at the target site, for an equal fraction of a lifetime, is expected to produce an equivalent carcinogenic response across species [O'Flaherty 1989; Travis et al. 1990; USEPA 1992]. The most appropriate concentration to use for interspecies scaling of a dermal carcinogen would be the concentration of the metabolically-activated form of the carcinogen at the target tissue – the dermis – after uptake through the epidermal layer. Estimating this concentration would ideally entail the development of a physiologically-based model of dermal uptake and metabolism, with appropriate physiological and metabolic parameters, for both humans and the animal species of interest. Short of this, the concentration of the parent compound, BaP, may be used as a practical surrogate measure of the concentration of the carcinogenic metabolite(s). Because the concentration of the parent material in contact with the dermis is simply the amount absorbed divided by the volume of the epidermal layer it is contained in, the concentration is expected to be approximately proportional to the total amount of material applied to the skin.

Adjustments for the physiological and metabolic differences between animal and human skin would be desirable, but in the absence of such information NIOSH supports the use of EPA's alternative dose metric 1, which is no interspecies adjustment of the daily applied dose, in preference to the other alternatives given.

2. The draft toxicological review contains a large volume of information, much of which is well done. NIOSH suggests that the following items be addressed before external review:

a) Many references cited in the body of the text are missing from the reference list, most notably Xu et al. [2010]. In chemical-specific charge question (A)1 of the *Draft Charge to External Reviewers,* EPA seeks confirmation from the reviewers that this toxicity study is an appropriate basis for the RfD.

b) The International Agency for Research on Cancer (IARC) classified benzo[a]pyrene as a Group 1 carcinogen (IARC [2010], Volume 92, page 773, http://monographs.iarc.fr/ENG/Monographs/vol92/mono92.pdf .)
Although there are multiple citations of IARC 2010 in the text, it does not appear in the Reference list.

c) The literature search strategy needs to be more clearly defined (page 2).

d) The draft review would benefit from consideration of other studies that have made use of specific assays – and it would be helped greatly by attention to detail with respect to interpretation of DNA-adduct studies and presentation of the references.

**Comments about 3.3 Metabolism:**

Pages 32 and 41: molecular epidemiologic studies that have tried to correlate "functional" polymorphisms with adduct levels or extent of cytochrome P450 induction/expression have

generally been inconsistent across different studies. Discussion of these studies individually, rather than from a review article, needs to be added.

Page 33 and elsewhere: BP is compared to cytochrome P450 induction potency of other compounds. However, some discussion of the literature that provides data on interindividual variation among humans would be of value; there are a considerable number of studies pertinent to this point.

Page 49, "matched controls": it is important to say what they were matched on.

**Comments about 4.1 Human Studies:**

Table 4-1 (pages 67-68): NIOSH recommends that this table be a much more extensive list of adduct studies.

Pages 69-70: NIOSH suggests a careful analysis of the literature regarding BP-adducts. Although the text has good points, certain fundamentals that might assist the IRIS analysis are lost or obscured. For example, we agree with the point that "$^{32}$P-postlabelling assays and immunological methods are the most commonly used." However, the statement (page 70, lines 33-35) that "…antibody's cross-reactivity with adducts originating from PAHs other than benzo[a]pyrene generally results in higher reported adduct levels than the $^{32}$P-postlabelling method which can isolate benzo[a]pyrene-DNA adducts" is incorrect because: 1) $^{32}$P-postlabelling methods do not "isolate" BP-adducts, in fact $^{32}$P-postlabelling provides no structural information at all; 2) the $^{32}$P-postlabelling of PAH-DNA adducts is a very inefficient process, despite claims to the contrary (see Manchester et al. [1990] *Carcinogenesis* 11: 553-559); and 3) optimal modification of DNA by BPDE in vitro to derive standard materials results in a modification level of approximately 1%. Calibration of most of the cited $^{32}$P-postlabelling assays and immunological methods is done with highly modified DNA that is cut with unmodified DNA (from salmon sperm). Such DNA behaves differently in these assays compared to DNA modified at levels close to environmental exposures (see Santella et al. [1988] *Carcinogenesis* 9: 1265-1269). Some or all of these issues need to be taken into account when interpreting these human studies.

Page 69: it is mentioned that mass spectral and other physical methods have been used but does not give any specific data. Various studies have presented highly specific and quantitative information that would be of value to this IRIS assessment.

Page 80, "matched controls": state what they were matched on.

**List of Abbreviations and Acronyms:** add DSF (dermal slope factor).

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**References**

O'Flaherty EJ [1989]. Interspecies conversion of kinetically equivalent doses. Risk Anal 9:587–598.

Travis CC, White RK, and Ward RC [1990]. Interspecies extrapolation of pharmacokinetics. J Theoret Biol 142:285-304.

USEPA (US Environmental Protection Agency) [1992]. Draft Report: A Cross-Species Scaling Factor for Carcinogen Risk Assessment Based on Equivalence of $mg/kg^{3/4}$/day. Fed Reg 57(109):24152(22). June 5.