Date: July 16, 2012

From: Centers for Disease Control and Prevention / Agency for Toxic Substances and Disease Registry

Subject: Comments on EPA's Toxicological Review of Benzo[a]pyrene

To: Environmental Protection Agency

General comments:
Overall, the toxicological review of benzo[a]pyrene is quite comprehensive. We feel the review does a good job of outlining the process used to arrive at each reference value. EPA has lowered the oral cancer slope factor from 7.3 to 1 $(mg/kg/day)^{-1}$ and determined that benzo[a]pyrene is "carcinogenic to humans. In addition, the review developed several new values including oral reference dose, reference concentration, inhalation unit risk and dermal cancer slope factor. These additions and changes will allow ATSDR to conduct more accurate and complete evaluations of exposure pathways involving benzo[a]pyrene.

It would be helpful to include a table that outlines the strengths and weaknesses of each of the studies presented and discussed throughout the document.

The review includes a detailed examination of benzo[a]pyrene DNA adducts and the work conducted in this area. However, benzo[a]pyrene also forms adducts with proteins such hemoglobin and serum albumin. Exposure to PAHs has been assessed by protein adduct dosimetry using benzo[a]pyrene as a model compound due to its well-known carcinogenic properties. There is a fair amount of research work that has been conducted in this area, but the authors fail to mention any of this work in the review. Proteins and DNA adducts are both considered useful biomarkers to assess exposure to benzo[a]pyrene in molecular and/or epidemiology studies. Perhaps the authors should consider whether an evaluation and discussion of benzo[a]pyrene protein adducts fit within the scope of this toxicological review.

It would also be helpful to clarify the setting and population of interest for both the chronic (oral) Rfd based on the 7-day exposure model by Chen et al (2012) and the chronic (inhalational) RfC based on the 10-day exposure model by Archibong et al (2002).

Other Comments:
Page XXX Line 9 "Evidence for specific DNA adducts"
Since the reactive intermediate benzo[a]pyrene diol expoxide (BPDE) can bind to guanine and adenine residues in DNA, language should be included to define/clarify what is meant by specific DNA adducts. Benzo[a]pyrene DNA adducts are formed when reactive metabolites of B(a)P, e.g., BPDE, bind to DNA. BPDE binds specifically with exocyclic amino groups of deoxyguanine (dG) and deoxyadenine (dA) residues.

However, the bulky DNA adducts that are primarily formed are the guanine adducts (10α-(deoxyguanosin-N^2-yl)-7α,8β,9β-trihydroxy-7,8,9,10-tetrahydrobenzo(a)pyrene or dG-N^2-BPDE)

Page 1-33 Line 32 Table 1-8
The work conducted by Matiasovic et al "Effects of Postnatal Exposure of Benzo[a]pyrene on the Immunity of Immature Rats" (2008) was not included in the table. In this work, Matiasovic et al determined the effect of benzo[a]pyrene on the developing immune system of immature rats.

Design: Newborn rats received different concentrations (0.1, 1.0 and 10.0 mg/kg/day) of benzo[a]pyrene in the first 14 days after birth.

Results: T cells in the spleen and mitogenic activity increased, decrease in expression of IL-4 and IFN-gamma was observed, spleenocytes were dose dependent, erythrocytes decreased in a dose dependent manner

Page 1-4, 1-11-12
Would suggest using birth cohort and not pregnancy cohort

Page 1-15 line 21 "the analytical methods were similar in the two studies"
Since the exposure measures have been shown to be method dependent, the method similarities and differences among the two studies should be detailed. It would be interesting to know how the limit of detection (LOD) compared between the two methods.

Page 1-19 Table 1-5
We suggest changing the column headers to Reference and Study Design

Page 1-30 Section 1.1.3. Line 15 "limited number of occupational studies particularly in coke oven workers"
Need to provide references for the limited number of studies involving coke oven workers. Also, there is no discussion of work conducted by Ming-Tsang Wu et al. "Relationship of Exposure to Coke Oven Emissions and Urinary Metabolites of Benzo[a]pyrene and Pyrene in Coke-Oven Workers (2002)

Page 1-59 Line 5 Summary of Metabolic Activation Pathways
Benzo[a]pyrene also forms adducts with proteins such hemoglobin and serum albumin. The protein adduct metabolic activation pathway has been well described in published manuscripts. It would be interesting to show both the DNA and the protein adduct pathway. Also, the stereochemistry of the reactive diolepoxide intermediate will determine the type of mutation that occurs. The (+) anti-diol expoxide intermediate is reportedly more carcinogenic than the (-) syn-diol epoxide intermediate. A more robust discussion of the mechanism of action as it relates to endpoints such as developmental and reproductive effects should be discussed and would help to strengthen this section.