

Thank you for the opportunity for ATSDR to provide opportunity to review and provide comments on the Technical Review of Benzo[a]pyrene EPA/635/R-16/331a dated November 2016.

This is a much needed document because the last one was written by EPA in late 1980s. It is a well-written document and the rationale for the conclusion is clearly presented.

EPA conducted a systematic, thorough and comprehensive literature search in 2012 and updated the searches in 2016 to ensure no new studies were published that change the conclusion of this document. About 21,000 references that consisted of epidemiological, human and animal studies were identified. Out of these, 700 references are cited in this review assessment document. The document has undergone extensive internal agency, public, and external reviews during 2013-2015.

This toxicological review is unique that for the first time EPA has derived multiple toxicity values other than cancer slope factor for B(a)P. Reference doses (RfDs) and reference concentrations (RfCs) were derived for both oral and inhalation routes of exposure. Additionally, organ specific RfDs were also derived which is a first for B(a)P. Such values will allow a full and realistic characterization of the toxicity of B(a)P. The concept of deriving multiple target organ specific toxicity values was proposed and published in 1997 by ATSDR (Mumtaz et. al., 1997). It has been well received by the risk assessment community and adopted by both US EPA and ATSDR mixtures guidelines (EPA, 2000; ATSDR, 2004). An additional improvement is that in deriving RfDs benchmark dose analysis was used to identify the point of departure.

Mumtaz, M.M., Poirier, K.A., and J.T. Colman (1997). Risk Assessment of Chemical Mixtures: Fine-Tuning the Hazard Index Approach. *J. Clean Technol. Environ. Toxicol Occup. Med.* Vol 6 (2): 189-204.

U.S. EPA (2000). Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides>

ATSDR (2004) Assessment of Joint Toxic Action of Chemical Mixtures <https://www.atsdr.cdc.gov/interactionprofiles/ipga.html>

The EPA derived the following toxicity values:

Organ Specific RfDs and overall RfD for benzo[a] pyrene

Effect Basis	Basis	RfD (mg/kg-d)	Confidence
Developmental	Neurobehavioral changes Chen et al. (2012)	3×10^{-4}	Medium
Reproductive	Decreased ovarian follicles and ovary weight Xu et al. (2010)	4×10^{-4}	Medium
Immunological	Decreased thymus weight and serum IgM De Jong et al. (1999)	2×10^{-3}	Low
Overall RfD	Developmental toxicity (including developmental neurotoxicity)	3×10^{-4}	

Organ Specific RfCs and overall RfC for benzo[a] pyrene

Effect	Basis	RfC (mg/m3)	Confidence
Developmental	Decreased embryo/fetal survival Archibong et al. (2002)	2×10^{-6}	Low-medium
Reproductive	Reduced ovulation rate and ovary weight Archibong et al. (2012)	3×10^{-6}	Low-medium
Overall RfC	Developmental toxicity	2×10^{-6}	