CHARGE TO EXTERNAL REVIEWERS FOR THE IRIS TOXICOLOGICAL REVIEWS OF

2,2',4,4'-Tetrabromodiphenyl Ether (BDE-47) CASRN 5436-43-1
2,2',4,4',5-Pentabromodiphenyl Ether (BDE-99) CASRN 60348-60-9
2,2',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153) CASRN 68631-49-2
2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl Ether (BDE-209) CASRN 1163-19-5

The U.S. EPA is conducting a peer review of the scientific basis supporting the human health assessments of BDE-47, BDE-99, BDE-153 and BDE-209 that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). The draft documents for the external peer review contain a description of the oral database, reference dose, and qualitative cancer assessment for BDE-47, BDE-99, BDE-153, and BDE-209, and a quantitative cancer assessment for BDE-209. Please provide detailed responses to the charge questions below.

GENERAL QUESTION

Are you aware of other published peer-reviewed toxicological studies not included in these Toxicological Reviews that could be of relevance to the health assessment of BDE-47, BDE-99, BDE-153 or BDE-209?

1. QUESTIONS RELATED TO THE DERIVATION OF THE REFERENCE DOSE FOR BDE-47, BDE-99, BDE-153 and BDE-209

1.1 Have the rationale and justification for deriving RfDs on the basis of the neurobehavioral toxicity studies been transparently and objectively described in the draft Toxicological Reviews of BDE-47, BDE-99, BDE-153 and BDE-209? Are there additional studies that should be considered for deriving the RfDs for any of the four PBDE congeners?

1.2 Do you agree or disagree with EPA basing the health assessment of BDE-47, BDE-99, BDE-153 and BDE-209 to a large extent on the Eriksson/Viberg neurobehavioral studies?

1.3 Are the Eriksson et al., 2001 (BDE-47), Viberg et al., 2004 (BDE-99), Viberg et al., 2003a (BDE-153) and the Viberg et al., 2003b (BDE-209) studies appropriate for determining the point of departure? Have the strengths and weaknesses of the Viberg and Eriksson studies been appropriately characterized and considered?

1.4 Have the most appropriate critical effect and point of departure been selected? And has the rationale for the point of departure been transparently and objectively described?

1.5 Have the rationale and justification for each uncertainty factor (UF) selected in the draft

Toxicological Reviews of BDE-47, BDE-99, BDE-153 and BDE-209 been transparently described? If the selected UFs are not appropriate, what alternative UFs would you suggest and what are the scientific rationales for those suggested? Does the database support the determinations of the RfDs for BDE-47, BDE-99, BDE-153, and BDE-209?

2. BODY BURDEN APPROACH

2.1 Are there adequate data for considering body burden as an alternative dose metric to administered doses in any of the RfD derivations?

2.2 Do you agree with the rationale described in the Toxicological Review of BDE-99 that the data on the window of susceptibility of the cholinergic receptors to BDE-99 tend to minimize body burden concerns?

3. QUESTIONS RELATED TO THE CARCINOGENICITY ASSESSMENT OF BDE-209

3.1 Is the weight of evidence for the carcinogenicity of BDE-209 in the draft Toxicological Review appropriately described? Are there additional studies that should be included?

3.2 Do the data support estimation of a cancer slope factor for BDE-209? If yes, is the rationale for the quantitative analysis objectively and transparently described, considering the uncertainty in the data and the suggestive nature of the weight of evidence? Have the rationale and justification for the use of linear low-dose extrapolation been objectively and transparently presented?

3.3 Are there alternative modeling approaches that should have been considered instead of or in addition to the linear low-dose extrapolation approach?

REFERENCES

Eriksson P, Jakobsson E, Fredriksson A (2001). Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? Environ Health Perspect. 109 (9):903-908.

U.S. EPA. (2005a) Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from:<http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA. (2005b) Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available from:<http://www.epa.gov/iris/backgr-d.htm>.

Viberg H, Fredriksson A, Eriksson P (2003a). Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. Toxicol. Appl. Pharmacol. 192(2):95-106.

Viberg H, Fredriksson A, Jakobsson E, Orn U, Eriksson P (2003b). Neurobehavioral derangements in adult mice receiving decabromodiphenyl ether (PBDE 209) during a defined period of neonatal brain development. Toxicological Sciences 76:112-120

Viberg H, Fredriksson A, Eriksson P (2004). Investigations of strain and/or gender differences in developmental neurotoxic effects of polybrominated diphenyl ethers in mice. Toxicol. Sci. 81:344-353.