

**Charge to External Reviewers for the IRIS Reassessment of the
Inhalation Carcinogenicity of Naphthalene
June 2004**

The U.S. EPA is conducting a peer review of the scientific basis supporting the reassessment of the inhalation carcinogenicity of naphthalene that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). The current IRIS assessment for the chronic health effects associated with naphthalene exposure was entered on the database in 1998. The release of the National Toxicology Program's 2-year inhalation study in rats (NTP, 2000) prompted this reassessment. The NTP studies (NTP, 1992, 2000) on naphthalene carcinogenesis are available at <http://ehp.niehs.nih.gov/ntp/docs/ntp.html>. Additional information is available on the NTP website (<http://ntp-server.niehs.nih.gov/Newhomeroc/11RoCBkgrnd.html>) regarding the consideration of naphthalene for the 11th Report on Carcinogens.

The documents for review contain revisions to the inhalation carcinogenicity assessment and other selected text. Changes made to the 1998 Toxicological Review of Naphthalene and IRIS Summary are noted as redlined or highlighted text. Appendix B (Benchmark Dose Modeling for the RfD/RfC Derivation) of the 1998 Toxicological Review has been removed for this review. Please provide detailed responses to the charge questions below.

Charge questions:

1) Metabolism of Naphthalene

Have the metabolic pathways for naphthalene been transparently described? Are there additional studies that have not been included that might be useful for the discussion of mode of action or human relevance of naphthalene carcinogenicity in animals?

2) Physiologically Based Pharmacokinetic (PBPK) Modeling

Have the available PBPK models been transparently described? Are there additional PBPK models available that have not been included?

3) Mode of Action of Carcinogenesis

Has the available information on the mode of action for inhalation carcinogenesis been transparently and objectively described? Are there additional studies that should be included?

4) Inhalation Carcinogenicity of Naphthalene

a) An assumption has been made that the nasal tumors in rats and lung tumors in mice are relevant to human carcinogenesis. Has this assumption been transparently and objectively described?

b) Naphthalene is described as likely to be carcinogenic to humans via the inhalation route of exposure based on the U.S. EPA 1999 Draft Revised Cancer Guidelines (www.epa.gov/ncea). Do the available data support this statement?

c) An inhalation unit risk has been derived utilizing benchmark dose modeling to define the point of departure of 10% extra risk followed by linear low-dose extrapolation below the point of departure.

1) The inhalation dosimetry equations used in the calculation of the human equivalent concentrations are for a category 1 gas (U.S. EPA, 1994). Is the explanation for the dosimetry choice in the derivation of the inhalation unit risk scientifically justified and transparently described?

2) Has support for the use of linear low dose extrapolation been objectively and transparently presented? Are there other modeling approaches that should have been considered instead of or in addition to the low dose linear extrapolation approach?

3) The inhalation unit risk is based upon the summed risks of developing olfactory neuroblastomas and respiratory epithelial adenomas in male rats derived from a time-to-tumor analysis. Is this approach scientifically justified? Are there other modeling approaches that should have been considered instead of or in addition to the approach taken? Has the best data set been chosen for derivation of the inhalation unit risk? Has the modeling been accurately and transparently described?