FACT SHEET: *Toxicological Review of Benzene - Noncancer Effects; April 2003*

Air pollution continues to be a widespread human health and environmental problem in the United States. Air pollution can cause premature death, cancer, long-term damage to respiratory and reproductive systems, and difficulty with breathing. Despite great progress in achieving cleaner, healthier air, as of 1999, about 62 million people were still breathing air that did not meet one or more of the health-based standards established by EPA. In addition, millions of tons of toxic pollutants are still being released into the air every year.

BACKGROUND: This review document completed by the National Center for Environmental Assessment (NCEA) in the Office of Research and Development (ORD), supplements and completes the human health assessment by describing the potential noncancer health hazards associated with environmental exposures to benzene. The review document also calculates an RfD and RfC that should protect all sensitive subgroups of humans from the adverse noncancer health effects of exposure to benzene.

The Office of Transportation and Air Quality (OTAQ), in EPA's Office of Air and Radiation (OAR), requested that NCEA provide an updated characterization of human health risk for both carcinogenic and noncancer effects from exposure to benzene. The cancer aspects have been previously discussed in the documents, *Carcinogenic Effects of Benzene: An Update* (April 1998) and the *Extrapolation of the Benzene Inhalation Unit Risk Estimate to the Oral Route of Exposure* (December 1999), which are available as summaries in the Integrated Risk Information System (IRIS) database.

Benzene, also known as benzol, is widely used as an industrial solvent, as an intermediate in chemical syntheses, and as a component of gasoline. The potential for human exposure is great. Inhalation exposure is the major route of exposure to benzene, although oral and dermal routes are also important. The toxicokinetics (absorption, distribution, metabolism and elimination) of benzene have been studied in humans and experimental animal species. Benzene is readily absorbed by both test animals and humans and is distributed among several body compartments. The parent compound is preferentially stored in fat, and the relative uptake appears to be dependent on the blood perfusion rates of tissues. The metabolism of benzene is required for expression of benzene toxicity.

Earlier drafts of this document received extensive internal and external peer review. An expert panel was convened in public session on October 28, 1998, to review an external review draft. Additional comments were received from the public during a public review and comment period. This final document reflects a consideration of all comments received during those reviews.

SUMMARY: Benzene exposure results in adverse noncancer health effects by all routes of administration to test animals. Hematotoxicity has been consistently reported to be the most sensitive indicator of noncancer toxicity both in limited studies in humans and experimental animals, with bone marrow as the principal target organ. Chronic exposure to benzene results in progressive deterioration of

hematopoietic function. Whether the hematotoxic and carcinogenic effects of benzene are due to a common mechanism has not been established. Lymphocytopenia has been shown to be the most sensitive indicator of benzene exposure in epidemiologic studies.
This document is limited to an assessment of the noncancer effects of exposure to benzene and was developed using several relevant risk assessment guidelines dealing with reproductive, developmental, neurotoxic, and other noncancer effects, including derivation of an oral reference dose (RfD) and inhalation reference concentration (RfC).

An RfC is an estimate of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The RfD is an estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The chronic inhalation RfC value calculated based on the human epidemiological data and using the benchmark dose (BMD) modeling approach yields an RfC of 3×10^{-2} mg/m^3 for lifetime exposure. Similarly, the chronic oral RfD, based upon the same human data and BMD modeling approach, yields an RfD of 4×10^{-3} mg/kg/day for a lifetime exposure. These values fall within the exposure range associated with a 10^{-4} cancer risk.

This toxicological review will serve as a scientific document for hazard identification and dose-response assessment in updating the noncancer health effects summary on benzene in the Integrated Risk Information System (IRIS) (http://www.epa.gov/IRIS).

DOCUMENT AVAILABILITY: The final document is available electronically on NCEA's website (http://www.epa.gov/ncea) under the *What's New* and *Publications* menus. A limited number of CDs and paper copies are available from EPA's National Service Center for Environmental Publications (NSCEP). To obtain copies, please contact NSCEP by telephone (1-800-490-9198 or 513-489-8190), by facsimile (513-489-8695), or by mail (P.O. Box 42419, Cincinnati, OH 45242-0419). Please provide your name and mailing address and the title and EPA number of the *Toxicological Review of Benzene - Noncancer Effects* (EPA/635/R-02/001, October 2002).

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