IRIS SUMMARY
Section II.B. Only

This is a draft revision to the Quantitative Estimate of Carcinogenic Risk From Oral Exposure section (II.B.) of the Benzene Summary report on IRIS.

.....II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

THIS SECTION HAS BEEN REVISED TO REFLECT THE CURRENT STATUS REGARDING THE QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE TO BENZENE.

.....II.B.1. SUMMARY OF RISK ESTIMATES

.....II.B.1.1. Oral Slope Factor - 1.5×10^{-5} to 5.5×10^{-5} per µg/kg-day

.....II.B.1.2. Drinking Water Unit Risk - 4.4×10^{-7} to 1.6×10^{-6} /µg/L

.....II.B.1.3. Extrapolation Method - Linear extrapolation of human occupational data

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	100 µg/L to 10^3 µg/L
E-5 (1 in 100,000)	10 µg/L to 10^2 µg/L
E-6 (1 in 1,000,000)	1 µg/L to 10 µg/L

.....II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type – leukemia
Test Species – human
Route – inhalation, occupational exposure
Reference – Rinsky et al., 1981, 1987; Paustenbach et al., 1993; Crump 1994; U.S. EPA, 1998; U.S. EPA, 1999.

The quantitative oral unit risk estimate is an extrapolation from the known inhalation dose-response to the potential oral route of exposure documented in Section II.C. The inhalation risk estimate is reported as a range, from 2.2×10^{-6} to 7.8×10^{-6} per µg/m^3. No relevant data exist in the published literature for absorption of benzene after ingestion in humans. Inhalation absorption is reasoned to be about 50% while that of ingestion is selected as 100% based upon a

review of the relevant human and animal literature (U.S. EPA, 1999). In the previous oral unit risk estimate it was assumed that absorption was equal for both the inhalation and oral routes of exposure (see Section VII, Revision History). The inhalation unit risk range, which is in units of risk per µg/m^3, is first converted to the oral slope factor, which is in units of risk per µg/kg-day, by assuming a standard air intake of 20 m^3/day, a standard body weight of 70 kg, and 50% absorption via inhalation. The drinking water unit risk was then calculated from the oral slope factor assuming a drinking water intake of 2 liters/ day. In calculating the drinking water concentrations for specific risk levels, the upper and lower end of the range round off to a single value.

This assessment of the oral unit risk range replaces the previous oral carcinogenicity assessment on IRIS which assumed a single unit risk estimate based upon the geometric mean of four maximum likelihood point estimates using pooled data from studies of Rinsky et al. (1981) and Ott et al.(1978) adjusted for the results of a study by Wong et al (1983).

.....II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The oral estimate range is derived from the inhalation unit risk range that is based on occupational data on leukemia from the epidemiological study of Pliofilm workers (Rinsky et al., 1981, 1987). These are discussed qualitatively in section II.A.2. and quantitatively in section II.C. The true cancer risk from exposure to benzene cannot be determined, because of uncertainties in the low-dose exposure scenarios and a lack of clear understanding of the mode of action. To extrapolate to the oral risk, the inhalation unit risk range is first converted to units of dose (µg/kg/day). Using the standard air intake factor of 20 m^3/day, the standard weight estimate of 70 kg. And the 50% absorption factor for inhalation exposure reasoned above (U.S. EPA, 1999), the dose from 1 µg/m^3 continuous daily exposure is:

$$1\ \mu g/m^3 * 20\ m^3/day * 0.5 * 1/70\ kg = 0.143\ \mu g/kg/day.$$

The risk estimate per µg/m^3 is then divided by this dose, to generate an oral slope factor in units of inverse dose:

$$risk/(\mu g/kg/day) = 1.54 \text{ X } 10^{-5} \text{ to } 5.45 \text{ X } 10^{-5}.$$

Assuming 100% absorption and a standard intake of 2 L/day, the concentration in drinking water that would produce a dose of 1 µg/kg/day is:

$$1\ \mu g/kg/day * 70\ kg * (2\ L/day)^{-1} = 35\ \mu g/L.$$

Thus, the oral unit risk, in units of risk/(µg/L) would be:

$$(1.54 \text{ X } 10^{-5} \text{ to } 5.45 \text{ X } 10^{-5})/35\ \mu g/L = 4.4 \text{ X } 10^{-7} \text{ to } 1.6 \text{ X } 10^{-6}/\mu g/L.$$

The range of estimates of 4.4 X 10^{-7} to 1.6 X 10^{-6} /µg/L is recommended, within which any value

will have equal scientific plausibility**.** The assumption is made that the leukemia effect is dependent on the absorbed dose. For inhalation, the metabolized dose is assumed to be 50% of the inhaled dose, as derived by Pekari et al (1992) from complete measurements on three male subjects. This conclusion is supported by earlier studies in humans (Hunter, 1966; Hunter, 1968; Hunter and Blair, 1972, Nomiyama and Nomiyama, 1974; Srbova et al., 1950; Teisinger et al., 1952 as cited in Fiserova-Bergerova et al., 1974 ; Yu and Weisel, 1998) and by a pharmacokinetic model developed by Bois et al (1996). In the absence of data in humans regarding the fraction of orally-ingested benzene that is metabolized, data from mice and rats (Sabourin, et al., 1987) suggests that there is a complete absorption of the dose received by corn oil gavage and intraperitoneally. In the absence of data to the contrary, it is reasonable to assume complete absorption of benzene ingested by humans based on animal data.

.....II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

The best available human epidemiological data for evaluation of the risk of cancer for exposure to benzene comes from occupational inhalation exposure studies (Rinsky et al., 1981, 1987). There is little human data regarding oral exposure to benzene. Route to route extrapolation is justified because similar toxic effects are observed in animals with either the oral or inhalation route of exposure to benzene (ATSDR, 1997) and toxicokinetic data are available from animal studies (Gerrity et al, 1990). Animal data also demonstrate that benzene is metabolized to the same products whether it is inhaled or ingested. Therefore, it is reasonable to extrapolate from inhalation dose-response to estimate an equivalent oral dose-response.

A rigorous method for route-to-route extrapolation that involves the development of a pharmacokinetic model to predict the concentration of the ultimate carcinogen in bone marrow has been proposed but has not been validated (Smith and Fanning, 1997). Furthermore, the nature of the distribution of benzene metabolites to the bone marrow is not well understood. The chemical species responsible for the induction of leukemia in animals and humans may involve more than one compound (Smith, 1996).

The best available absorption efficiencies across pulmonary and gastrointestinal barriers provide an informed basis to adopt reasonable values for benzene absorption. The oral slope factor is derived from the inhalation slope factor currently documented in the IRIS database (Section II.C.). Since no exposure data on human ingestion of benzene are available but it is known that complete gastrointestinal absorption occurs in the rat and mouse study as reported by Sabourin et al (1987), it is reasonable to assume complete absorption in humans. However, it is clear from numerous studies of pulmonary absorption in humans that absorption of benzene via the inhalation route is incomplete.

There is a general consensus in the literature supporting the use of a 50% absorption via inhalation and not using default assumptions that assume both exposure routes have equivalent absorption efficiencies. Based upon the Pekari et al (1992) study, which EPA has judged to be the most scientifically sound , an absorption factor of 50% was chosen for this exercise.

In the absence of evidence to the contrary, key studies support the reasonableness of

extrapolating from inhalation to oral cancer risk. The calculations use standard EPA conversion factors for air and water intake and informed assumptions about the amount of absorption of benzene from oral and inhalation exposure.

REFERENCES (TO BE ADDED TO SECTION VI.C. CARCINOGENICITY ASSESSMENT REFERENCES)

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[ ] indicates references already in IRIS file on inhalation unit risk assessment. Therefore, they do not have to be integrated with the references already in IRIS on benzene.