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Extrapolation of the Benzene Inhalation Unit Risk Estimate to the Oral Route of Exposure

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ABSTRACT

A simple method for extrapolation of benzene-induced cancer risk from the inhalation to oral route is proposed. The method is based on the relative efficiency of benzene absorption across routes of exposure, especially pulmonary and gastrointestinal barriers. There exists substantial literature on pulmonary absorption in humans and a few laboratory animal species. Data on oral absorption in humans are lacking; hence extrapolation is based on gastrointestinal absorption studies in several experimental animal species. Currently, available physiologically based pharmacokinetic (PBPK) animal models are not useful for human risk extrapolation. A review of the relevant literature suggests absorption efficiencies of 50% and 100% for inhalation and oral routes of exposure, respectively. Application of these absorption factors to the current inhalation unit risk range of $2.2 \times 10^{-6} – 7.8 \times 10^{-6}$ per $\mu g/m^3$ results in a proposed range for the oral unit risk of 4.4×10^{-7} to $1.6 \times 10^{-6}/\mu g/L$.

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PREFACE

This document is a source document for updating the oral cancer unit risk estimate for benzene in the Integrated Risk Information System (IRIS).

In the development of this document, the scientific literature has been reviewed, key studies have been evaluated and summarized, and the carcinogenicity and related information are qualitatively and quantitatively characterized. The relevant scientific literature has been reviewed through April 1999.

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1. INTRODUCTION

The best available human epidemiological data for evaluation of cancer risk for benzene derive from studies of occupational inhalation exposure. In order to apply the results of risk estimates derived from these studies to the estimation of cancer risk arising from oral exposure to benzene, a rationale for route-to-route extrapolation needs to be established.

A workshop organized by EPA and the ILSI Risk Science Institute concluded that route-to-route extrapolation for risk assessment is appropriate when similar toxic endpoints are observed with both routes of exposure and when toxicokinetic data are available (Gerrity and Henry, 1990). Because of a lack of data on orally exposed humans, it cannot be concluded that leukemia and related hematopoietic endpoints are associated with the oral route of exposure. However, in animal models, similar cancers and hematotoxic endpoints occurred in several studies of both oral and inhalation exposure (ATSDR, 1997). Experimental animal data also demonstrate that benzene is metabolized to the same products, whether inhaled or ingested. Therefore, it is reasonable to extrapolate from inhalation to oral cancer risk.

Extrapolation from an inhalation to an oral slope factor in the earlier IRIS entry for benzene was based on conversion between the standard intake factors for air and water (U.S. EPA, 1999). The extent of absorption after oral exposure was assumed, by default, to be equivalent to absorption from inhalation exposure. A data-based extrapolation would improve upon this default approach.

A scientifically rigorous method for route-to-route extrapolation involves the development of a pharmacokinetic model to predict the concentration of the ultimate carcinogen in bone marrow (the target tissue for benzene's carcinogenic effects) under a variety of different human exposure scenarios. There are currently several inadequacies in the scientific database required for this approach. No pharmacokinetic models that include metabolism and distribution to the bone marrow are available that have been adequately validated for humans (Smith and Fanning, 1997). A major difficulty is that the particular chemical species responsible for the induction of leukemia in benzene-exposed people and animals is not known with certainty; leukemogenesis may well involve more than one metabolite or combination of metabolites (Smith, 1996).

Most experts agree that benzene metabolites, or by-products of their formation, are responsible for benzene leukemogenesis. This suggests that extrapolation between routes of exposure could be based on a dose defined as the total quantity of benzene metabolized in the body after uptake of equivalent amounts, a somewhat simpler metric than delivered dose of the unknown ultimate carcinogenic compound(s). However, the kinetics of metabolite formation and clearance after inhalation, ingestion, or dermal exposure of benzene are not known for humans. The many uncertainties involved in using animal-based models to predict dosimetry for humans

may preclude a risk assessment application for PBPK models dependent on animal-derived data. Using a PBPK model developed primarily with high-dose animal data is not likely to improve the accuracy of risk estimates based on human data.

Therefore, a simple approach to route-to-route extrapolation is perhaps the most scientifically defensible approach at this time. This report summarizes published literature addressing the absorption of benzene after inhalation exposure in humans and laboratory animals, and after oral exposure to animals. No relevant data were located for absorption of benzene after ingestion in humans. Using the best estimates of the relative absorption efficiencies across the pulmonary and gastrointestinal barriers as the basis of route-to-route extrapolation, an oral slope factor is derived from the inhalation slope factor currently documented in the IRIS database.

2. ORAL ABSORPTION

Benzene is absorbed by rabbits, hamsters, mice, and rats following administration by oral gavage. In an early study in rabbits, 90% of the radioactivity from a single bolus dose was recovered in urine and exhaled air (Parke and Williams, 1953). Medinsky et al. (1984) determined gastrointestinal absorption by comparing the percentage of administered dose excreted in urine, feces, and exhaled air after gavage to the percentages resulting from intraperitoneal (i.p.) injection to rats. Furthermore, Sabourin and colleagues administered radiolabeled benzene orally, by corn oil gavage, and intraperitoneally to rats and mice (Sabourin et al., 1987). The details of the study are as follows:

Sprague-Dawley and F344/N rats and $B6C3F_1$ mice (3-4 per dose) were dosed by oral gavage (0.5 through 300 mg/kg body weight) or i.p. injection (0.5 or 150 mg/kg) with [^{14}C] benzene (approximately 10 uCi per rat and 2 uCi per mouse. The [^{14}C] benzene was administered in corn oil. Urine and feces were collected at 4, 8, 16, 24, 32, and 48 hr after dosing.

The percentages of the dose excreted by each route were similar following gavage or i.p. injection. Gastrointestinal absorption of benzene was determined by comparing excretion routes following oral or i.p. administration at the same dose and was essentially 100% for F344/N rats, Sprague-Dawley rats, and $B6C3F_1$ mice at 0.5 or 150 mg/kg body weight. Therefore, the dose of benzene absorbed is equal to the amount administered by gavage. At all dose levels tested, most of the [^{14}C] benzene and metabolites were excreted in the urine and in the expired air. In both rats and mice, at doses below 15 mg/kg > 80% of the ^{14}C was excreted in the urine. In F344/N and Sprague-Dawley rats, the excretion of ^{14}C in the expired air following oral or ip administration plateaued between 16 and 24 hr. However, in $B6C3F_1$ mice, no further expiration of ^{14}C occurred beyond 4 hr. Cumulative urinary excretion of ^{14}C plateaued at 16 to 32 hr in all three species.

Cumulative urinary ^{14}C excretion displayed large animal variability at early time points due to the voluntary nature of urination.

Urinary ^{14}C can be used as a measure of net [^{14}C] benzene metabolism. Less than 5% of the ^{14}C in urine from animals treated with 0.5-150 mg/kg [^{14}C] benzene was extractable into ethylacetate, indicating that >95% of the ^{14}C was due to water-soluble metabolites. For F344/N rats and B6C3F$_1$ mice, metabolism of [^{14}C] benzene, as indicated by urinary ^{14}C, appeared to be linearly related to dose up to 15 mg/kg. For both species, nonlinearity of metabolite formation versus dose became apparent somewhere between 15 and 50 mg/kg and an increasing amount of the administered [^{14}C] benzene was eliminated in the expired air above 15 mg/kg. At doses up to 50 mg/kg, F344/N rats and B6C3F$_1$ mice excreted almost equal amounts of benzene equivalents per kg body weight in the urine. In F344/N rats, urinary ^{14}C continued to increase with dose above 50 mg/kg, albeit not linearly above 15 mg/kg. In B6C3F$_1$ mice, total metabolite formation (urinary ^{14}C) plateaued above 50 mg/kg at 0.42 mmol benzene equivalents/kg body weight. This may have been due in part to the faster elimination of [^{14}C] benzene in the expired air by mice compared with that by rats. In mice, 71% of the initial dose of [^{14}C] benzene was eliminated in the exhaled air at the 150 mg/kg dose, whereas in rats only 50% was exhaled at this concentration.

Results of gastrointestinal absorption studies indicated that, for all three species (F344/N and Sprague-Dawley rats and B6C3F$_1$ mice), virtually 100% of an orally administered dose of benzene was absorbed. The small amount of ^{14}C found in feces following i.p. injection of [^{14}C] benzene may be due to biliary excretion.

Sabourin et al., (1987) suggested that absorption of benzene could be determined based on the method of Medinsky et al. (1984) using the equation:

$$\text{Percentage absorption} = 100 - F_{po} + F_{ip}[(U_{po} + A_{po})/(U_{ip} + A_{ip})].$$

In this formula, F is the percentage of the initial dose in feces, U is the percentage of the initial dose in urine, A is the percentage of the initial dose in the expired air, po refers to gavage (per os)-treated animals, and i.p. refers to intraperitoneally injected animals.

In a recent study, rats, mice, and hamsters were treated by oral gavage (in corn oil) with a range of benzene doses that overlapped, but extended lower than the dose range used in the Sabourin study cited above (Mathews et al., 1998). Each dose for rats, mice, and hamsters contained 12–26, 4–21, and 3–22 uCi radiolabel, respectively. Additionally, all dose formulations contained an appropriate amount of unlabeled benzene and corn oil in a single dose volume of 5 mL/kg (rats and hamsters) or 25 mL/kg (mice) and these doses were administered by intragastric gavage. Results of the study demonstrated that benzene was readily absorbed, metabolized, and

eliminated primarily in urine by each species studied. However, the routes of elimination were somewhat altered by dose. At the high dose of 100 mg/kg a significant portion of the dose was eliminated in breath. Elimination of a dose of 100 mg/kg in breath ranged from 22% in mice to 50% in the rats. A complete absorption from the gastrointestinal tract was confirmed in all three species. Both studies report a greater proportion of metabolites excreted in urine at low doses, with a shift to greater amounts of unmetabolized benzene excreted in exhaled air at high doses. This result suggests that saturation of metabolism occurs at doses greater than approximately 100 mg/kg; however, at the oral doses at which humans are likely to be exposed, the animal results suggest a linear increase in total metabolite production with exposure level.

In humans, oral exposure occurs by ingestion of benzene-contaminated food or water. No relevant animal studies are available that allow a comparison of absorption between gavage and drinking water administration. Theoretically, benzene ingested in drinking water could be subject to volatilization loss from the stomach, which would be suppressed by the oil vehicle used in the animal gavage experiments. On the other hand, it might be expected that a greater proportion of large bolus doses would escape absorption, and pass through in the feces, while smaller doses would be better absorbed. The fact that essentially complete absorption was observed even at high gavage doses in the Sabourin et al. (1987) and Mathews et al. (1998) studies suggests that, in the absence of data to the contrary, it is reasonable to assume complete absorption of benzene ingested by humans.

3. DERMAL ABSORPTION

Several studies conducted both with humans and experimental animals indicate that benzene is readily absorbed through the skin from both liquid and vapor phases and the percentage of absorption of the applied doses is usually less than 1% (Franz, 1983, 1984; Maibach and Anjo, 1981; Susten et al., 1985). In in vivo experiments on four human volunteers, when 0.0026 mg/cm^2 of C^{14}-benzene was applied to forearm skin, approximately 0.05% of the applied dose was absorbed (Franz, 1983, 1984). Absorption was rapid, with more than 80% of the total excretion of the absorbed dose occurring in the first 8 hours after application. Calculations were based on urinary excretion data and no correction was made for the amount of benzene that evaporated from the applied site before absorption occurred. In addition, the percentage of absorbed dose excreted in urine that was used in the calculation was based only on data from rhesus monkeys and may not be accurate for humans. Tsuruta (1989) reported that dermal absorption of benzene increased linearly with dose in hairless mice exposed to benzene vapors and estimated that skin absorption of benzene by humans would be 3.7% that of inhalation exposure at the same concentration.

4. PULMONARY ABSORPTION

Pulmonary absorption of volatile organic compounds is not expected to be complete; some portion of the inhaled concentration is exhaled from the lung without entering systemic circulation. Experimental evidence confirms incomplete absorption of benzene in both animals and humans.

4.1. RATS AND MICE

In the Sabourin study cited above, rats and mice were also exposed to benzene by inhalation (Sabourin et al., 1987). The results are summarized in Table 1. Mice and rats were exposed for 6 hours to 13, 29, and 130 ppm benzene by inhalation. Rats were also exposed to 260 and 870 ppm for 6 hours, while mice were exposed to one high dose of 990 ppm for 6 hours. The total inhaled dose of benzene was computed from the exposure concentration and measured breathing rate. The amount of benzene retained was then computed as a fraction of this quantity, based on the amount of benzene remaining in the carcass or excreted in urine and feces. Benzene taken up but subsequently excreted in exhaled air is not counted in the absorbed fraction. This definition of absorption is distinct from that used in the subsequent discussion of human data, but may be examined for rough comparison. Therefore, this absorption information from animal data may underestimate true exposure in humans. The percent of inhaled benzene retained in rats and mice will be found in Table 1.

4.2. HUMANS

There is a significant database on benzene in exhaled breath of humans exposed to benzene in occupational, environmental, or experimental situations. Occupational and environmental exposure is generally quite variable from individual to individual and over time. This variability renders estimation of the actual exposure received quite complicated in many situations. Therefore, we focus here on studies of controlled human exposures to known concentrations of benzene for known duration.

Table 1. Percent of inhaled benzene retained in rats and mice

Exposure concentration (ppm)		Average percentage retained after 6 hours (n=3)	
Rats	***Mice***	***Rats***	***Mice***
13	11	33	50
29	29	44	52
130	130	23	38
260	--	22	--
870	990	15	9.7

Source: Sabourin et al., 1987.

Chamber studies are often designed to study the excretion of benzene and/or its metabolites in exhaled air. While useful information concerning half-life of benzene in the body and elimination kinetics can be obtained from the postexposure period, concurrent measurements of exposure concentration (Cinh) and benzene in exhaled air (Cexh) are necessary to compute instantaneous absorption factors. It should be noted that a fraction of the benzene absorbed may not be metabolized, thus, underestimating absorption. For this report, the percent of benzene absorbed is defined simply as: 100 * (Cinh - Cexh)/Cinh. In some of the publications we reviewed, concentration data were reported in different formats, and the numbers were converted to the units in Table 2 to facilitate comparison across studies. The results are summarized in Table 2.

4.2.1. Hunter and Colleagues (Hunter, 1966; Hunter, 1968; Hunter and Blair, 1972)

In the first paper of this series, absorption of 47% was reported for one male subject exposed for 24 minutes to a concentration “a little above the threshold value of 25 ppm” (Hunter, 1966). In the next paper, one male subject exposed for 2 and 4 hours to approximately 30 ppm absorbed 55%-60% of the inhaled concentration (Hunter, 1968). Hunter and Blair (1972) exposed 5 male subjects for 2-3 hours to concentrations ranging from about 30 to 100 ppm. However, inhaled and exhaled air concentrations are not reported for the time during exposure, except for one subject (Table 2). The time of sampling was not given; neither was it clear whether the data represent a single sample or an average of multiple samples. For this single subject, exposed over a period of 5 days to concentrations ranging from 21 to 32 ppm, the percent absorbed (computed as above) ranged from 53% to 63%. It is not clear whether this is a different subject from the previous report.

4.2.2. Nomiyama and Nomiyama (1974)

Nomiyama and Nomiyama (1974) determined both “retention” and “uptake” of benzene.

Table 2. Absorption of inhaled benzene in humans

Study	Percent absorbed, average (range)	Exposure concentration	Exposure duration	Number of subjects	Number of samples per exposure period
Teisinger et al., 1952, as cited in Fiserova-Bergerova et al., 1974	48%	n.a.	5 hr	14	n.a.
Hunter, 1966	47%	25-30 ppm	24 min.	1	n.a.
Hunter, 1968	(55%-60%)	approx. 30 ppm	2 hr, 4 hr	1 (2 exposures)	n.a.
Hunter and Blair, 1972	(53%-63%)	21-32 ppm	3-4 hr	1 (10 exposures)	1
Nomiyama and Nomiyama, 1974	30% (SD 6.7)	52-62 ppm	4 hr	6	3
Pekari et al., 1992	52% (SD 7.3) 48% (SD 4.3)	1.7 ppm 10 ppm	4 hr 4 hr	3 3	6 6
Srbova et al., 1950	50%-62% (one subject) 20%-50% (reported group range after 2 hours)	100 ppm 47-110 ppm	90 min 2-3 hr	1 23	7 every 15 min
Yu and Weisel, 1998	64% (range: 48%-73%)	32-69 ppm (in tobacco smoke)	30 min 120 min	3 3	4 7

n.a. = not available.

Their calculation of retention is equivalent to the definition of absorption used in this report. Six subjects, three male and three female, were exposed to benzene concentrations ranging from 52 to 62 ppm for 4-hour periods. Exhaled air was sampled every hour. The authors report average retention to be 30.2%. This figure is somewhat lower than the other studies discussed here. However, the data indicate that a potential explanation is that absorption was averaged over the 3, 3.5, and 4-hour time points only. The percent absorption was time-dependent in these experiments: absorption was high early in exposure, and approached a steady state only after 3 hours. According to the data plotted by the authors, the average absorption at the 1-hour time point was approximately 60% for women and 45% for men. A decrease to approximately 43% and 35%, respectively, occurred at the 2-hour time point.

4.2.3. Pekari et al. (1992)

Pekari et al. (1992) developed a reliable and specific method for biologically monitoring benzene in blood. Subjects were exposed to benzene in air at 10 cm^3/m^3 and 1.7 cm^3/m^3. The

amount of benzene absorbed into the body was then estimated from the average difference in the concentration of inhaled and exhaled air. It was 48.0% + 4.3% (SD) for the high exposure and 52.0% + 7.3% (SD) for the low exposure. Earlier methods based on urinary metabolites were nonspecific. Although the experimental exposure study group included just three healthy nonsmoking male workers, 16 blood specimens were drawn over a 24-hour period for each individual. In addition, blood specimens from another group of three smoking male and six nonsmoking subjects were used to account for the confounding influence of smoking in estimating occupational exposure to low levels of benzene. The sensitivity of the assay for benzene in the blood enabled the investigators to trace exposure down to a benzene concentration of 1 cm^3/m^3 or less in the air, making this a good analytical method.

4.2.4. Sherwood (1988)

A single male subject was studied. In reporting their results, the authors stated that the methods used allowed uptake to be "roughly estimated," however, they do not report the uptake fraction. The method for collecting exhaled air during the exposure period did not involve an actual breath sample, but was based on the concentration of benzene in the outlet of a self-pressurized blouse in which the exposure occurred. Because of these problems, this study is not listed in Table 2.

4.2.5. Srbova et al. (1950)

This was the largest study, reporting on 27 exposures to 23 subjects. Exposure concentrations ranged from 47 to 100 ppm, and exposure durations were for 2-3 hours. Exhaled air samples were taken every 15 minutes. Unfortunately, specific absorption data are given for only one experiment. The authors report that, in general, absorption was greatest in the first 5 minutes but decreased to 20%-60% after 1 hour and to 20%-50% after a second hour. For the one subject on whom data were reported, absorption ranged from 50% to 62% over one exposure period in which samples were taken at 5, 15, 30, 45, 60, 75, and 90 minutes. Higher figures for absorption resulted from samples early in the exposure period; a steady decrease was observed as exposure progressed.

4.2.6. Teisinger et al. (1952) (data reported in Fiserova-Bergerova et al., 1974)

This study was published in Czech (Teisinger et al., 1952, cited in Fiserova-Bergerova et al., 1974) and subsequently translated into French (Teisinger et al., 1955, also cited in Fiserova-Bergerova et al., 1974). Neither of these publications were reviewed for this report. Figure 2 from Fiserova-Bergerova et al. (1974) gives the data from the Teisinger study in graphic form. A

mean absorption of about 47%, with standard error encompassing approximately 43%-53%, can be estimated from the figure. These data represent the average of measurements from 14 subjects exposed for 5 hours and sampled toward the end of the exposure period. The exposure level is not clear from the 1974 Fiserova-Bergerova et al. (1974) report; however, it has been cited as being 100 ppm (Travis et al., 1990a).

4.2.7. Yu and Weisel (1998)

In this recent study, benzene concentration in inhaled and exhaled air was reported for three female subjects, each sampled at four time points during one to three exposure episodes. However, the exposures were to sidestream tobacco smoke, rather than pure benzene. Smoke was generated from burning cigarettes in room air, resulting in variable benzene concentrations during exposure and incomplete mixing. Exposure sessions were of 30 or 120 minutes duration. Benzene concentrations ranged from 32 to 69 ppm. The mean percent absorbed in eight experiments was 64%, with a range of experiment averages from 48% to 73%. While several studies have reported that absorption is higher at the outset of inhalation exposure, there was no significant difference between the shorter and longer duration experiments in this study.

5. DISCUSSION OF ROUTE-TO-ROUTE ABSORPTION

The data summarized above clearly indicate that absorption of benzene from the inhalation route is incomplete. But regardless of the route of administration, unmetabolized benzene has been recovered from exhaled air. In addition to that which is not absorbed, even absorbed benzene can be released, unmetabolized, into the alveoli and exhaled. We consider the Pekari et al. (1992) study to be the most technically sound because of its use of modern experimental methods and collection of a large number of samples per subject. On the basis of Pekari et al. (1992) and other studies referred to above, we recommend the use of a 50% absorption factor for inhalation exposure to benzene. There is very good overall agreement among the studies, with most supporting an absorption factor close to 50%.

Some corroboration of the 50% factor can be found in the literature on exhaled air measurements arising from occupational and environmental exposure. For example, exhaled breath measurements from 46 control subjects from an occupational study, who had low background exposure to benzene (median 19 ng/L), suggested an average absorption of 55% (Perbellini et al., 1988). In most studies of this sort, however, exhaled air samples were collected in the postexposure period. The concentration of benzene in exhaled air falls very rapidly upon removal from exposure, so postexposure samples cannot be compared to those taken during

exposure. Wallace et al. (1993) reported an absorption fraction of 70% for benzene, based on measurements of exhaled air for "several hundred" nonsmokers in the TEAM studies. The inhaled air concentration used to compute this fraction was the average concentration over the preceding 12 hours. Using observed measureents of breath and preceding 12-hr air exposures for several hundred nonsmokers in the TEAM studies, Wallace and his coworkers (1993) calculated a fraction of the air concentration are about 0.2 to 0.3 for benzene.

A recent PBPK modeling study applied data on benzene in blood and exhaled air supplied by Pekari and colleagues (1992) to a model describing benzene disposition in the body (Bois et al., 1996). After fitting model parameters to the data set, the model predicted that 57% of benzene in inhaled air is metabolized in the body. Since at low exposure levels, a majority of the absorbed benzene is metabolized rather than excreted unchanged, the 57% figure can be roughly compared to the 50% absorption factor that Pekari and colleagues (1992) estimated from their measurements. Until the model is further validated by application to other human data, we recommend the use of actual measurements.

The general agreement of the animal and human data provides additional support for the exposure results from Pekari et al. (1992). The two low exposure concentrations in Table 1 overlap with the range of concentrations tested in human studies. At these lower concentrations, inhalation absorption efficiency is similar in animals and humans.

An estimate of 50% absorption by inhalation is also consistent with other estimates in the literature. ACGIH (1998) cites the conclusion in Rusch et al. (1977) that approximately 46% of inhaled benzene is absorbed in humans. Another estimate, based on the studies of Hunter (1966, 1968), Nomiyama and Nomiyama (1974), and Srbova et al. (1950) cited above, was 47% (Owen, 1990). The latter estimate was adopted by MacIntosh and colleagues for use in a recent population-based exposure model for benzene (MacIntosh et al., 1995). An analysis of short-term exposure limits for benzene assumed 50% absorption by inhalation (Paxman and Rappaport, 1990). Since dermal absorption was found to be usually less than 1% of applied dose (Franz, 1983, 1984; Maibach and Anjo, 1981; Susten et al., 1985), the effect of dermal absorption upon the total absorbed from all routes is considered minimal. Thus, there is a general consensus in the literature that supports replacing the default assumption of equivalent absorption by oral and inhalation routes by an inhalation absorption estimate of 50%.

6. POTENTIAL ISSUES

6.1. DOSE-DEPENDENCY OF ABSORPTION

Animal studies covered a wide range of inhalation concentrations. A decrease in the fraction of the exposure concentration absorbed was observed in both mice and rats as inhaled

concentration increased from 29 to 130 ppm (Table 1), suggesting that metabolic saturation for animals may begin in this concentration range. In a recent inhalation study in Sprague-Dawley rats, a shift in clearance from chamber air was seen between concentrations in a much lower range, raising the possibility that metabolism becomes saturated at concentrations as low as 10 ppm (Yoshida et al., 1998). At steady state, uptake is equal to clearance from the blood. Saturated metabolism would result in reduced apparent absorption efficiency of benzene due to limitations of blood benzene concentrations. While air benzene concentrations used in controlled human exposure studies collectively covered nearly two orders of magnitude, no dose dependency can be observed when the studies are taken together. There is some indication that the high exposure levels (up to 110 ppm) used in the Srbova et al. (1950) study may have resulted in lower absorption (the lower end of the range was 20%); however, the analytical methods in this early work may not be accurate. It is not clear whether the lack of evidence of saturation in the human studies is because exposure levels did not reach those used in animal studies or because substantial interstudy and interindividual variability obscures any possible relationship among these studies, with their generally very small sample sizes. The results of the TEAM studies may indicate that higher fractions of inhaled concentrations are absorbed at very low doses.

6.2. TIME-DEPENDENCY OF ABSORPTION

Data from several of the chamber studies indicates that there is a lag time between the onset of exposure and the time at which steady-state blood concentration is reached. Most studies averaged the absorption percentages from early and late exposure phases together. In an excretion study (not considered above, because only postexposure exhaled air was sampled) it was found that benzene accumulated over a 5-day period in which a subject was exposed each day (Berlin et al., 1980). This suggests that the chamber studies may not be of sufficient length to reach a true equilibrium. Pulmonary absorption efficiency in chronically exposed people, or workers exposed for longer intervals than were subjects of chamber studies, could be lower than suggested by the relatively short-term exposure studies discussed above. A lower inhalation absorption efficiency would result in an inversely proportionate higher unit risk estimate.

6.3. GENDER DEPENDENCE OF ABSORPTION

The Nomiyama and Nomiyama (1974) study found that women had higher initial absorption of benzene, although at equilibrium the percent absorbed was similar to men. The Yu and Weisel study was performed on female subjects and reported some of the highest estimates of absorption. Sato et al. (1975) exposed 5 men and 5 women to 25 ppm benzene for 2 hours. Exhaled air concentrations were measured for the postexposure period only. Clearance of benzene appeared to be slower in women, a finding the authors attributed to differences in body

fat. It is possible that the observations of Yu and Weisel (1998), and Nomiyama and Nomiyama (1974) can be explained by a slower approach to steady-state conditions in women because of more extensive partitioning into fat. Because of the paucity of detailed data on female subjects, however, whether there are significant gender differences in absorption kinetics remains unclear.

6.4. METABOLISM AND TOXICOKINETICS

The metabolism of benzene is required for expression of benzene toxicity. Evidence has recently been reviewed by several investigators (Snyder and Hedli, 1996; Ross, 1996; Rangan and Snyder, 1997) and has been summarized (U.S. EPA, 1998). Metabolites postulated as responsible for benzene toxicity include the following: (i) benzene oxide; (ii) open- ringed metabolites such as trans, trans muconaldehyde; (iii) polyphenolic metabolites such as hydroquinone, catechol, 1,2,4-trihydroxy-benzene, and their quinone oxidation products; and (iv) combination of metabolites.

The characterization of a single benzene metabolite or a combination of metabolites that is/are responsible for the pathological effects of benzene has not been well established to date. A clear concern remains that low-level exposure to benzene may potentially result in acute myelogenous leukemia (AML) in humans. A better understanding of the role of benzene and its metabolites and their dosimetry in target organs would be of significant value in characterizing the exposure and dose-response relationship. In particular, this involves the collection of data on the concentration of key metabolites in bone marrow, including phenol, hydroquinone, muconaldehyde, and benzene oxide, and how it may relate to the level of benzene to which an individual is exposed. There are significant uncertainties if any nonlinearity in the exposure dose-response relationship and shape of the curve for these metabolites is to be assumed for benzene-induced AML, particularly in extrapolating from high-level exposures to low-level environmental exposures of concern.

There have been several attempts to develop PBPK models to refine the understanding of the interactions of benzene metabolism and toxicity. The first PBPK model for benzene was developed by Sato (Sato and Nakajima, 1979; Sato, 1988). Subsequently, more PBPK complex models have been developed, to take into account differences in benzene metabolism between species and individuals, using both experimental data and simulations, by Medinsky et al. (1989), Travis et al. (1990a, b), and Bois et al. (1991a).

The Medinsky model (Medinsky et al., 1989) was one of the first PBPK models to be developed for benzene. It was based on an earlier PBPK model developed by Ramsey and Anderson (1984). The model describes and predicts the fate of benzene and determines if differences in the metabolic pathways between rats and mice could explain the differences in toxicity between these species. Bois et al. (1991b) applied the data of Rickert et al. (1979) to the Medinsky model and found that the Medinsky model tended to overestimate benzene uptake.

Since the original model was published, additional compartments have been added to reflect the advancing understanding of benzene metabolism, and specific biochemical and toxicokinetic parameters have been refined to reflect age, sex, and species-specific differences (Schlosser et al., 1993; Seaton et al., 1994; McMahon et al., 1994; Kenyon et al., 1995). Using metabolic parameters derived from human liver samples in vivo, the steady-state concentration of phenol predicted by the model varied sixfold (0.38-2.17 nM) and predicted hydroquinone concentrations varied fivefold (6.66-31.44 nM). The predicted concentrations for mice were higher than the range for humans, but the rat values were within the predicted concentrations for humans. On this basis the authors suggested that the rat may be a good model for humans with respect to tissue dosimetry for these benzene metabolites.

Travis et al. (1990a, b) developed a model to describe the pharmacokinetics of benzene in rats, mice, and humans. Metabolism of benzene was assumed to follow Michaelis-Menten kinetics in all species and was assumed to occur primarily in the liver, and to a lesser extent in the bone marrow. Physiological parameters were derived from the literature, and metabolic parameter values were determined by fitting model output to available measured data, using visual inspection as a measure of fit. Model simulations for humans were compared to data from Berlin et al. (1980), Nomiyama and Nomiyama (1974), Sherwood (1972), Sato et al. (1975), and Teisinger and Fiserova-Bergerova (1955). The Travis model successfully simulated benzene in blood and exhaled air from several of these studies. However, the Travis model is limited because it does not predict the kinetics of benzene metabolites (Bois et al., 1991b). The quantity of phenol in urine from one older study (Teisinger and Fiserova-Bergerova, 1955) was modeled, but the quality of the fit is unclear.

The model developed by Bois and Paxman (1992) provided strong evidence that the exposure rate had a strong influence on the rate of formation of several important metabolites of benzene. The Bois and Paxman (1992) model was validated against the data of Cassidy and Houston (1984), Sabourin et al. (1987, 1988, 1989), and Sawahata and Neal (1983). Simulation results indicated that the model may over- or underestimate the level of urinary metabolites. More recent efforts on improving the original PBPK model of Bois and Paxman (1992) have focused on defining the physiological pharmacokinetic parameter distributions needed to develop models useful in risk assessment (Spear et al., 1991; Spear and Bois, 1994; Watanabe and Bois, 1996; Bois et al., 1996). Bois recently applied his model to the human data collected by Pekari and colleagues (1992). By using a statistical fitting process that explicitly accounts for interindividual variability and by using a Bayesian approach, posterior distributions were derived for model parameters. The median estimate for the fraction of benzene metabolized after inhalation exposure in this study was 52%, the mean was 57%, and the 95% confidence interval was 47%–67%. Since the fraction metabolized is expressed as a fraction of the benzene taken

into the lungs via alveolar air, much of the unmetabolized benzene is simply not absorbed. This finding is not inconsistent with an absorption efficiency of approximately 50%.

While current PBPK models discussed above may provide insights as to putative toxic metabolites and potential biochemical mechanisms, they are not sufficiently developed as to reduce scientific uncertainty (Medinsky et al., 1995, 1996), particularly concerning the prediction of metabolite formation in humans. One of the most important next steps is to apply the existing models to data on human metabolism, such as data resulting from biomonitoring of workers for urinary metabolites.

Thus, we conclude that, while they are important tools for understanding dosimetry in animals, these models are not sufficiently refined to provide a significant advantage for extrapolation between oral and inhalation exposure to humans. The key areas for improvement appear to be the inclusion of the kinetics of the putative toxic metabolites of benzene or their stable precursors. If benzene metabolites, such as hydroquinone/benzoquinone or muconaldehyde, or benzene oxide are the toxic species for bone marrow toxicity and AML, then PBPK models need to include descriptions of their kinetics and validated to predict the risk from exposure to benzene.

Furthermore, one could potentially examine the relationship between benzene dosimetry and benzene-induced effects in experimental animals that might be considered precursor events of human risk for AML. However, there is no confirmed animal model for AML induced by inhalation or oral exposure to benzene, thus, such modeling efforts are of limited use for human risk extrapolation. Potential role of- and dosimetry data on trans, trans-muconaldehyde (Smith, 1996) and/or benzene oxide (Lindstrom et al, 1997) in relation to benzene-induced toxicity in bone marrow remain to be examined.

7. EXTRAPOLATION FROM INHALATION TO ORAL RISK

EPA's quantitative estimate for the cancer risk associated with inhalation exposure to benzene was recently updated (U.S. EPA, 1998). The new inhalation unit risk estimate is reported as a range, from 2.2×10^{-6} to 7.8×10^{-6} per $\mu g/m^3$ (U.S. EPA, 1999). The standard factors (70 kg person breathing 20 m^3 per day and drinking 2 liters of tap water per day) pertain to the typical adult population as evaluated in the late 1970s when the EPA risk assessment procedures were established. With the publication of the Exposure Factors Handbook (U.S. EPA, 1997), information about the population variability of drinking water and air and food intakes became widely available. It showed that the mean tap-water intake across the U.S. population is 1.4 liters per day, and that 2 liters per day is the 84th percentile of the intake,

meaning that 84% of the population drinks 2 liters per day or less (U.S. EPA, 1997). For inhalation rates, the mean value is 15 cubic meters per day for males and 11 cubic meters per day for females (U.S. EPA, 1987), but the population distribution was not presented. For body weights, the mean values are 76 kilograms for males, 65 kilograms for females, and 72 for the sexes combined. To extrapolate to 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 determined above, 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 range is then divided by this dose, to generate an oral slope factor in units of inverse dose:

$$\text{risk}/(\mu g/kg/day) = 2.2 \times 10^{-6}/0.143\ \mu g/kg/day \text{ to } 7.8 \times 10^{-6}/0.143\ \mu g/kg/day$$
$$= 1.54 \times 10^{-5} \text{ to } 5.45 \times 10^{-5} \text{ per } \mu g/kg/day$$

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:

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

Note: This estimate is a risk factor for ingested benzene, and is not sufficient to account for total exposure to drinking water. For development of a drinking water safe concentration, the risk due to inhalation of volatilized benzene from drinking water and to dermal uptake must be added to the ingestion risk (Beavers et al., 1996; Lindstrom et al., 1994). Development of a corrected intake factor to account for total exposure to drinking water is beyond the scope of this report.

In using the standard values for the following risk estimate, it should be recognized that we are not accounting for the population variability of these factors and that we are over-estimating the mean intake rates of air and tap water, although 70 kilograms is close to the population mean body weight. If we had attempted to estimate the population mean risk for tap water contamination, those values would be 70% of those estimated below, and the inhalation

risks for males and females would be 75% and 55%, respectively, of those estimated below.

If one assumes a 20% respiratory absorption rate, the lowest value in a group of subjects (range 20% to 50%), found in one study (Srbova et al., 1950), then the oral unit risk range becomes 1.10×10^{-6} to 3.89×10^{-6}. This may represent an upper bound on the risk range.

7.1. FURTHER QUESTIONS, AND COMMENTS ON DATABASE ADEQUACY

A substantial literature provides information on pulmonary absorption in humans. The animal study selected for this report provides excellent information in two species for both inhalation and oral absorption. However, data on oral absorption from drinking water exposure would be a useful addition.

While the human data demonstrate good agreement indicating that approximately one-half of inhaled benzene is absorbed into the bloodstream at exposure concentrations between 1 and 100 ppm, considerable interindividual variability was observed in all studies that reported on multiple subjects. Many factors, including activity level, pulmonary health, and metabolic clearance, are likely to influence the amount of benzene actually taken up in a diverse population exposed by the inhalation route. To date, characterization of the extent of variability is limited.

The simple absorption ratio approach taken to route-to-route extrapolation here cannot account for differences in disposition of benzene after it crosses the pulmonary or gastrointestinal barrier. First-pass metabolism of ingested benzene may have significant effects on the dose of benzene metabolites that reaches the target bone marrow cells (Sabourin et al., 1989). Leukemogenic metabolites may be produced more efficiently after ingestion, but on the other hand, rapid clearance of benzene and metabolites after ingestion may be a mitigating factor. The data are inadequate to address these questions for humans at this time, but a variety of biomarkers of benzene exposure can help to address questions of internal dose of benzene metabolites. Biomarker data, together with further development of PBPK models, using human data to define parameters wherever possible, may provide improved dose metrics for benzene risk assessment in the near future.

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