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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 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. 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 November 1998.

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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 occupational 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 U.S. 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 et al., 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, although different exposure routes affect the disposition and metabolism of benzene (Sabourin et al., 1989). 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, 1999a). 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 compound (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 and ingestion 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 at present.

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. Finally, further data needs are noted.

2. GASTROINTESTINAL ABSORPTION

Benzene is absorbed in 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). Sabourin and colleagues administered radiolabeled benzene orally, by corn oil gavage, and intraperitoneally (i.p.) to rats and mice (Sabourin, 1987). Doses of 0.5, 5, 14, 50, and 150 mg/kg were given to F344 rats and B6C3F1 mice by the oral route; i.p. doses were 0.5 and 150 mg/kg. Exhaled air, urine, feces, pelt, and body tissues were collected for analysis of radioactivity over the 48 hours following dosing. Gastrointestinal absorption was determined by comparing the percentage of administered dose excreted in urine, feces, and exhaled air after gavage to the percentages resulting from intraperitoneal injection (i.p.) administration (Medinsky et al., 1984):

$$\% \text{ absorbed} = 100 - F_{oral} + F_{i.p.}[(Ur_{oral} + Exh_{oral})/(Ur_{i.p.} + Exh_{i.p.})]$$

(F is percent recovered in feces, Ur is percent in urine, and Exh is percentage in exhaled air.) Using this approach, the authors observed essentially equivalent absorption by oral and i.p. routes, suggesting complete absorption after gavage. Experiments on Sprague-Dawley rats were carried out at the 0.5 and 150 mg/kg doses only, and yielded similar results.

In a recent study, rats, mice, and hamsters were treated by oral gavage 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). Nearly 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. 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.

3.1. 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

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.

definition of absorption is distinct from that used in the subsequent discussion of human data, but may be examined for rough comparison. See Table 1 for retention data.

3.2. 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.

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 post-exposure period, concurrent measurements of exposure concentration (Cinh) and benzene in exhaled air (Cexh) are necessary to compute instantaneous absorption factors. 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 by us to the units above to facilitate comparison across studies. The results are summarized in Table 2.

3.2.1. 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

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.

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%-63%. It is not clear whether this is a different subject from the previous report.

3.2.2. Nomiyama and Nomiyama (1974)

The authors determined both "retention" and "uptake" of benzene. 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 in Figure 2 of the publication 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 in the figure, 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.

3.2.3. 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 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.

3.2.4. Sherwood (1988)

A single male subject was studied, and the author stated that the methods used allow uptake to be "roughly estimated," but the uptake fraction is not reported. 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.

3.2.5. Srbova et al. (1950)

This was the largest study, reporting on 27 exposures to 23 subjects. Exposure concentrations ranged from 47-100 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 (computed from data in the first two columns of the table entitled "Experiment 27," using the formula specified above). Higher figures for absorption resulted from samples early in the exposure period; a steady decrease was observed as exposure progressed.

3.2.6. 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., 1990).

3.2.7. 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.

4. DISCUSSION OF INHALATION 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 following administration by any route of entry. 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. 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. Based on this study, 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 control subjects from an occupational study, who had low background exposure to benzene, 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 nonsmokers in the TEAM studies (Table 1 of the publication). The inhaled air concentration used to compute this fraction was the average concentration over the preceding 12 hours, and thus the data were not included in Table 2 of this report.

A recent PBPK modeling study applied data on benzene in blood and exhaled air supplied by Pekari and colleagues 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 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). 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%.

5. POTENTIAL ISSUES

5.1. DOSE-DEPENDENCY OF ABSORPTION

Animal studies covered a wide range of inhalation concentrations. A decrease in absorption was observed in both mice and rats as inhaled concentration increased from 29 to 130 ppm (Table 1). 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, suggesting the possibility of saturation of metabolism as low as 10 ppm (Yoshida et al., 1998). Saturated metabolism would be expected to result in reduced absorption of benzene due to slower clearance 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 higher absorption at very low doses.

5.2. 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 post-exposure 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). Higher blood levels would limit further uptake. This suggests that 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.

5.3. GENDER DEPENDENCE OF ABSORPTION

The Nomiyama et al. (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, and Nomiyama 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. 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, 1999b). 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 $\mu g/m^3$ 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 $\mu g/m^3$ is then divided by this dose, to generate an oral slope factor in units of inverse dose:

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

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:

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

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.

6.1. 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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