Benzene; CASRN 71-43-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Benzene

File First On-Line 03/01/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	04/17/2003
Inhalation RfC (I.B.)	yes	04/17/2003
Carcinogenicity Assessment (II.)	yes	01/19/2000

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Benzene
CASRN — 71-43-2
Last Revised — 04/17/2003

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg/day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the IRIS Background Document for an elaboration of these concepts. The U.S. EPA has evaluated this

substance for potential human carcinogenicity. A summary of that evaluation is found in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased lymphocyte count (Human occupational inhalation study; Rothman et al., 1996)	BMDL = 1.2 mg/kg/day	300	1	4.0×10^{-3} mg/kg/day

*Conversion factors: MW = 78.11. Assuming 25ºC and 760 mm Hg, BMCL (mg/m^3) = 7.2 ppm x MW/24.45 = 23 mg/m^3. $BMCL_{ADJ}$ = 23 mg/m^3 x 10 m^3/20 m^3 x 5 days/7days = 8.2 mg/m^3. The BMDL was derived by route-to-route extrapolation with the assumptions that inhalation absorption was 50% and oral absorption was 100% in the dose range near the BMC. $BMDL_{ADJ}$ = 8.2 mg/m^3 x 20 m^3/day x 0.5 ÷ 70 kg = 1.2 mg/kg/day. (The original BMC was based on a benchmark response of one standard deviation change from the control mean.)

I.A.2. Principal and Supporting Studies (Oral RfD)

The RfD is based on route-to-route extrapolation of the results of benchmark dose (BMD) modeling of the absolute lymphocyte count (ALC) data from the occupational epidemiologic study by Rothman et al. (1996), in which workers were exposed to benzene by inhalation. A comparison analysis based on BMD modeling of data from the National Toxicology Program's (NTP's) experimental animal gavage study (NTP, 1986) was also conducted. In addition, comparison analyses using the lowest-observed-adverse-effect levels (LOAELs) from the Rothman et al. (1996) and NTP (1986) studies were performed.

Rothman et al. (1996) conducted a cross-sectional study of 44 workers exposed to benzene and 44 age- and gender-matched unexposed controls. Twenty-one of the 44 subjects in the exposed and control groups were female. Mean (standard deviation) years of occupational exposure to benzene were 6.3 (4.4), with a range of 0.7-16 years. Benzene exposure was monitored by organic vapor passive dosimetry badges worn by each worker for a full workshift on 5 days within a 1-2 week period prior to collection of blood samples. The median 8-hour time-weighted average (TWA) benzene exposure concentration for all exposed workers was 31 ppm (99 mg/m^3). The exposed group was subdivided into two equal groups of 22 subjects: those exposed to greater than the median concentration and those exposed to less

than the median concentration. The median 8-hour TWA exposure concentration was 13.6 ppm (43.4 mg/m^3) for the low-exposure group and 91.9 ppm (294 mg/m^3) for the high-exposure group.

Six hematological measurements were evaluated: total white blood cell (WBC) count, ALC, hematocrit, red blood cell (RBC) count, platelet count, and mean corpuscular volume (MCV). All six parameters were significantly different in the high-benzene exposure group (>31 ppm) when compared to controls. ALC, WBC count, RBC count, hematocrit, and platelets were all significantly decreased, and MCV was significantly increased. ALC was the most sensitive endpoint; it was reduced from 1.9 x 10^3/µL blood in controls to 1.6 x 10^3/µL (p<0.01) in the <31 ppm group and to 1.3 x 10^3/µL (p<0.001) in the group exposed to >31 ppm benzene. The ALC was also significantly reduced (1.6 x 10^3/µL; p=0.03) in a subgroup of 11 workers exposed to a median 8-hour TWA of 7.6 ppm (24 mg/m^3) benzene. For additional details about this study see Section I.B.2.

BMD modeling of the ALC data of Rothman et al. (1996) yielded a benchmark concentration (BMC) of 13.7 ppm (8-hr TWA) and a BMCL (the 95% lower bound on the BMC) of 7.2 ppm (8-hr TWA) for the default benchmark response of one standard deviation change from the control mean (see Section I.B.2 for details of the analysis). Converting the units and adjusting for continuous exposure results in a $BMCL_{ADJ}$ of 8.2 mg/m^3. [According to the Ideal Gas Law, concentration in mg/m^3 = concentration in ppm x MW/24.45 at 25ºC and 760 mm Hg. Thus, BMCL (mg/m^3) = 7.2 x 78.11/24.45 = 23.0 mg/m^3. $BMCL_{ADJ}$ = 23.0 mg/m^3 x 10 m^3/20 m^3 x 5 days/7 days = 8.2 mg/m^3, where 10 m^3 is the default human occupational volume of air inhaled in an 8-hour workshift, and 20 m^3 is the default human ambient volume of air inhaled in a 24-hour day (U.S. EPA, 1994).]

In the support document for the benzene cancer assessment on IRIS (U.S. EPA, 1999), EPA provided a simple method for extrapolation of benzene-induced cancer risk from the inhalation to the oral route. The same method is applied here for noncancer (hematopoietic) effects. The method is based on the relative efficiency of benzene absorption across routes of exposure, especially pulmonary and gastrointestinal barriers. An inhalation absorption rate of 50% and an oral absorption rate of 100% were used to calculate the absorbed benzene dose. These values are based on human inhalation absorption studies and the study by Sabourin et al. (1987) that compared inhalation and oral absorption in rats and mice. The authors found that during a 6-hour inhalation exposure, the retention of [^{14}C]benzene decreased from 33 ± 6% to 15 ± 9% for rats and from 50 ± 1% to 10 ± 2% for mice as exposure concentration increased from 26 to 2,600 mg/m^3 (10 to 1,000 ppm). In the same study, gastrointestinal absorption of benzene administered by gavage was >97% for doses between 0.5 and 150 mg/kg body weight. At oral doses below 15 mg/kg, >90% of the ^{14}C excreted was in the urine as non-ethyl acetate-extractable material. At higher doses, an increasing percentage of the orally

administered benzene was exhaled unmetabolized. Thus, in the dose range represented by the BMCL from the study by Rothman et al. (1996), absorption of a comparable oral dose was assumed to be 100%. See also U.S. EPA (1999) for more details about the route-to-route extrapolation of benzene inhalation results to oral exposures.

To calculate an equivalent oral dose rate, the $BMCL_{ADJ}$ is multiplied by the default inhalation rate, multiplied by 0.5 to correct for the higher oral absorption, and divided by the standard default human body weight of 70 kg: 8.2 mg/m^3 x 20 m^3/day x 0.5 ÷ 70 kg = 1.2 mg/kg/day. The RfD is then derived by dividing the equivalent oral dose by the overall uncertainty factor (UF) of 300: RfD = equivalent oral dose/UF = 1.2 mg/kg/day ÷ 300 = 4 x 10^{-3} mg/kg/day. The overall UF of 300 comprises a UF of 3 for effect-level extrapolation, 10 for intraspecies differences (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies (see Section I.A.3).

For comparison, an RfD was also calculated based on the LOAEL of 7.6 ppm (8 hr TWA) from the Rothman et al. (1996) study (see Section I.B.2). Converting the units and adjusting for continuous exposure results in a $LOAEL_{ADJ}$ of 8.7 mg/m^3. Then the equivalent oral exposure is calculated as above: 8.7 mg/m^3 x 20 m^3/day x 0.5 ÷ 70 kg = 1.2 mg/kg/day. The equivalent oral exposure is then divided by an overall UF of 1000 to obtain the RfD: 1.2 mg/kg/day ÷ 1000 = 1 x 10^{-3} mg/kg/day. The combined UF of 1000 represents UFs of 10 to account for the use of a LOAEL because of the lack of an appropriate no-observed-adverse-effect level (NOAEL), 10 for intraspecies differences in response (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies. The value of 1 x 10^{-3} mg/kg/day is in good agreement with the value of 4 x 10^{-3} mg/kg/day calculated from the BMDL (the 95% lower bound on the BMD).

A comparison RfD derivation was also performed using the results of the NTP (1986) experimental animal gavage study. In that study, F344 rats and B6C3F1 mice of both sexes were administered benzene by gavage, 5 days/week for 103 weeks. Male rats (50/group) were administered doses of 0, 50, 100, or 200 mg/kg, and females (50/group) were administered doses of 0, 25, 50, or 100 mg/kg. B6C3F1 mice (50/sex/group) were administered doses of 0, 25, 50, or 100 mg/kg. Blood was drawn from 10 randomly preselected animals per species/sex/dose group at 12, 15, 18, and 21 months, as well as from all animals at the terminal kill at 24 months. Additional groups of 10 animals of each sex and species were administered benzene for 51 weeks at the same doses of the 103-week (2-year) study, and blood was drawn at 0, 3, 6, 9, and 12 months. This study identified a LOAEL of 25 mg/kg for leukopenia and lymphocytopenia in female F344 rats and male and female B6C3F1 mice and 50 mg/kg in male F344 rats. These were the lowest doses tested, and thus no NOAEL was identified.

Reductions in lymphocyte count was the critical effect, and attempts were made to model the dose-response relationships using a BMD modeling approach. Modeling was performed for each dataset in two data groupings within which the datasets are comparable (6- and 9-month; and 12-,15-,18-, and 21-month), and ranges of results are presented. Each of these datasets had at most 10 animals/dose, so the dose-response results are not very robust. The males of each species exhibited more dramatic and consistent reductions in lymphocyte count, but it was not clear a priori which species was more sensitive; therefore, dose-response analyses were performed for both the male mouse and the male rat.

The continuous linear, polynomial, and power models in EPA's Benchmark Dose Modeling Software (version 1.20) were used for the modeling. The software estimates the parameters using the method of maximum likelihood. Most of the data were supralinear (i.e., the magnitude of the reductions in lymphocyte count decreased with increasing unit dose), and it was necessary to transform the dose data according to the formula $d' = \ln(d+1)$ in order to fit the available models. The results are summarized in Table 1. For each dataset, the selected model was chosen based on the lowest Akaike's Information Criterion (AIC) value, with consideration of the graphical display, as suggested in EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000). For selecting between models within a family of models, for example, between a linear and a two-degree polynomial model, consideration was given to the log-likelihood values to evaluate the statistical significance of adding an extra parameter. There was substantial variability in these data, but it appeared to be random and not amenable to modeling. Therefore, constant variance was assumed for all the models, although in some cases the variances failed the test for homogeneity.

In the absence of a clear definition for an adverse effect for this endpoint, a default benchmark response of one standard deviation change from the control mean response was selected, as suggested in the draft technical guidance document. This definition of the benchmark response is highly sensitive to the substantial variability in data such as these, and thus the benchmark response itself is not very robust. The usefulness of this default definition would be strengthened by the use of a larger dataset of historical control data, but such data were not located. The software uses the estimated "constant" standard deviation as the standard deviation for all the group means. The 95% lower confidence limits (BMDLs) on the BMDs are calculated using the likelihood profile method.

The results shown in Table 1 suggest that the male rat is more sensitive than the male mouse to lymphocyte count reductions from exposure to benzene in this NTP gavage bioassay because the ranges of BMDs/BMDLs are substantially lower for the male rat, especially for year 2. The ranges for the male rat are fairly tight, and the models selected provide good fits to all the male rat datasets. However, all but one of the calculated BMDs for the male rat are over an order of magnitude below the lowest exposure dose of 50 mg/kg. Ideally, BMDs should be

closer to the low end of the range of observation, that is, the range of the actual exposure doses, to reduce the impacts of model selection and the uncertainties inherent in extrapolating to lower doses.

Nevertheless, data from two drinking water studies provide support for selecting a BMD in this range. These two studies were of shorter duration and used fewer experimental animals than the NTP (1986) study; however, they do provide dose-response data for BMD modeling, and they also have the advantage of being drinking water studies; thus the benzene exposure scenario is more relevant to human oral benzene exposures. In one study, Hsieh et al. (1988) exposed male CD-1 mice (five/group) to 0, 8, 40, or 180 mg/kg/day benzene in drinking water for 28 days. Hematological effects were observed at all exposure levels. BMD modeling of the ALC yielded a BMD of 2.2 mg/kg/day and a BMDL of 1.4 mg/kg/day, based on a linear model with transformed doses and a benchmark response of one standard deviation change from the control mean, as above. In the second study, White et al. (1984) exposed female B6C3F1 mice to 0, 12, 195, or 350 mg/kg/day benzene in drinking water for 30 days. BMD modeling of the ALC (five to six mice/group) resulted in a BMD of 11.6 mg/kg/day and a BMDL of 5.3 mg/kg/day (also based on a linear model with transformed doses and a benchmark response of one standard deviation change from the control mean, as above).

Table 1. BMD modeling results for NTP (1986) male mouse and male rat lymphocyte counts, with transformed dose data

Dataset	Model	Variance Homogeneity	Fit	BMD[a] (mg/kg)	BMDL[a] (mg/kg)
		Male Mouse			
6-month	two-degree polynomial	ok	borderline p=0.047	19.68	6.57
9-month	linear	no	yes, p=0.35	9.07	4.05
year 1 range				9.07-19.68	4.05-6.57
12-month	linear	ok	yes, p=0.30	3.74	2.32

Dataset	Model	Variance Homogeneity	Fit	BMD[a] (mg/kg)	BMDL[a] (mg/kg)
15-month	power	no	yes, p=0.31	47.46	18.55
18-month	power	no	borderline p=0.09	28.93	13.99
21-month	power	no	yes, p=0.15	23.34	5.80
year 2 range				3.74-47.46	2.32-18.55
			Male Rat		
6-month	power	ok	yes, p=0.30	9.92	4.52
9-month	linear	no	yes, p=0.11	3.71	2.30
year 1 range				3.71-9.92	2.30-4.52
12-month	linear	no	yes, p=0.22	1.34	0.95
15-month	linear	ok	yes, p=0.93	1.34	0.95
18-month	linear	no	yes, p=0.22	2.73	1.74
21-month	linear	ok	yes, p=0.54	1.69	1.10
year 2 range				1.34-2.73	0.95-1.74

[a]Unadjusted animal dose in mg/kg, after transforming the results back according to the formula dose = exp(transformed dose) – 1. (The BMD was based on a benchmark response of one standard deviation change from the control mean.)

The results in Table 1 from BMD modeling of the male rat ALC data from the NTP (1986) study show the lowest BMDL of about 1 mg/kg at three time points in the second year; thus this was selected as the point of departure for an RfD calculation. Adjusting for exposure 7 days/week yields a $BMDL_{ADJ}$ of 0.7 mg/kg/day. This value is divided by an overall UF of 1000 to obtain the RfD: RfD = 0.7 mg/kg/day ÷ 1000 = 7×10^{-4} mg/kg/day. The overall UF of 1000 comprises UFs of 3 for effect-level extrapolation, 10 for interspecies extrapolation for oral studies, 10 for intraspecies variability, and 3 for database deficiencies. This RfD value is in reasonably good agreement (within an order of magnitude) with the RfD of 4×10^{-3} mg/kg/day derived from the Rothman et al. (1996) human inhalation study.

For comparison purposes, an RfD can also be derived from the LOAEL of 25 mg/kg identified for hematological effects in the NTP (1986) study (there was no NOAEL). Adjusting from 5-day to 7-day exposure yields a $LOAEL_{ADJ}$ of 18 mg/kg/day, which can be used to calculate an RfD for benzene as follows: RfD = $LOAEL_{ADJ}$ ÷ UF = 18 mg/kg/day ÷ 3000 = 6×10^{-3} mg/kg/day, where the combined UF of 3000 is made up of component factors of 10 for LOAEL-to-NOAEL extrapolation, 10 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database deficiencies. This value is in good agreement with the RfD of 4×10^{-3} mg/kg/day calculated from the BMD analysis of the Rothman et al. (1996) human data.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 300 for the BMCL-oral-equivalent from the Rothman et al. (1996) study.

First, because the BMC is considered to be an adverse effect level, an effect level extrapolation factor analogous to the LOAEL-to-NOAEL UF is used. EPA is planning to develop guidance for applying an effect level extrapolation factor to a BMD. A factor of 3 will be used in this analysis, based on the professional judgement that, although the BMD corresponds to an adverse effect level at the low end of the observable range, the endpoint is not very serious in and of itself. Decreased ALC is a very sensitive sentinel effect that can be measured in the blood, but it is not a frank effect, and there is no evidence that it is related to any functional impairment at levels of decrement near the benchmark response. For a more serious effect, a larger factor, such as 10, might be selected. Second, a factor of 10 was used for intraspecies differences in response (human variability) as a means of protecting potentially sensitive human subpopulations. Third, a subchronic-to-chronic extrapolation factor was applied because the mean exposure duration for the subjects in the principal study was 6.3 years, which is less than the exposure duration of 7 years (one-tenth of the assumed human life span of 70 years) that has been used by the Superfund program as a cut-off for deriving a subchronic human reference dose (U.S. EPA, 1989). Furthermore, the exposure duration varied from 0.7 years to 16 years. However, because the mean exposure duration was near the borderline of what would be considered chronic (i.e., 6.3 years vs. 7 years), a value of

3 (vs. 10) was felt to be appropriate for the UF. Finally, a UF of 3 was chosen to account for database deficiencies because no two-generation reproductive and developmental toxicity studies for benzene are available. Therefore, an overall UF of 3 x 10 x 3 x 3 = 300 is used to calculate the chronic oral RfD.

For the comparison analysis based on the Rothman et al. (1996) $LOAEL_{ADJ}$-equivalent oral dose rate value of 1.2 mg/kg/day, the following UFs were selected: a factor of 10 for use of a LOAEL due to lack of an appropriate NOAEL, a factor of 10 for intraspecies variability, a factor of 3 for subchronic-to-chronic extrapolation, and a factor of 3 for database deficiencies, as above. Hence, an overall UF of 10 x 10 x 3 x 3 = 1000 was used in the comparison analysis.

For the comparison analysis based on the $BMDL_{ADJ}$ calculated from BMD modeling of the male rat data from the NTP (1986) gavage study, the following UFs were used: a UF of 3 for effect-level extrapolation, which is analogous to the LOAEL-to-NOAEL extrapolation factor, because the BMC is considered an adverse effect level; a UF of 10 for interspecies extrapolation for oral studies; a UF of 10 for intraspecies variability; and a UF of 3 for database deficiencies. Thus, an overall UF of 3 x 10 x 10 x 3 = 1000 was used in this comparison analysis.

Finally, for the comparison analysis based on the LOAEL from the NTP (1986) gavage study, the following UFs were used: 10 for LOAEL-to-NOAEL extrapolation, 10 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database deficiencies. Therefore, an overall UF of 3000 was used in this comparison analysis.

I.A.4. Additional Studies/Comments (Oral RfD)

Benzene is toxic by all routes of administration. Hematotoxicity and immunotoxicity have been consistently reported to be the most sensitive indicators of noncancer toxicity in both humans and experimental animals, and these effects have been the subject of several reviews (Aksoy, 1989; Goldstein, 1988, Snyder et al., 1993; Ross, 1996; U.S. EPA, 2002). The bone marrow is the target organ for the expression of benzene hematotoxicity and immunotoxicity. Leukocytopenia has been consistently shown to be a more sensitive indicator of benzene toxicity in experimental animal systems than anemia, and lymphocytopenia has been shown to be an even more sensitive indicator of benzene toxicity than overall leukocytopenia. Neither gastrointestinal effects from oral exposure nor pulmonary effects due to inhalation exposure have been reported. (see Section I.B.4 for a more detailed summary of benzene toxicity).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.4 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The overall confidence in this RfD assessment is medium. The principal study of Rothman et al. (1996) was well conducted, and the availability of good-quality human data for a sensitive endpoint eliminates the uncertainty associated with basing the RfD on experimental animal data. A dose-response relationship was established between ALC and benzene air concentration and benzene urine metabolites. Six blood parameters measured (ALC, WBC count, RBC count, hematocrit, platelets, and MCV) were significantly different in the high-benzene-exposure group when compared with controls. However, only the ALC was reduced in a subgroup of 11 subjects exposed to a median 8-hour TWA of 7.6 ppm benzene, suggesting that this exposure level may be at the low end of the range of benzene exposures eliciting hematotoxic effects in humans.

In addition, the RfD of 4×10^{-3} mg/kg/day obtained from route-to-route extrapolation of the BMD modeling results from the Rothman et al. (1996) study is in good agreement with the value of 1×10^{-3} mg/kg/day based on the oral equivalent LOAEL. The RfD is also in good agreement with the value of 7×10^{-4} mg/kg/day, based on BMD modeling of the male rat ALC data from the NTP (1986) chronic rodent gavage study and the value of 6×10^{-3} mg/kg/day based on the LOAEL from the NTP (1986) study.

With continuous endpoints such as hematological parameters, there is uncertainty about when a change in a parameter that has inherent variability becomes an adverse effect. Other uncertainties explicitly recognized in the quantitative derivation of the chronic oral RfD include intraspecies variability (to accommodate sensitive human subgroups), the applicability of the subchronic inhalation data to chronic oral exposures, and database deficiencies due to the lack of a two-generation reproductive/developmental toxicity study for benzene.

Route-to-route extrapolation was used to estimate oral equivalent doses from inhalation exposures resulting from analysis of the Rothman et al. (1996) occupational data. In experiments conducted to compare the metabolite doses to the target organ following oral or inhalation exposure, Sabourin et al. (1987, 1989) found that there was no simple relationship between the two routes of exposure. All published experimental animal models of the in vivo metabolism and disposition of benzene have used the physiologically based approach to pharmacokinetics, and they conclude that formation of metabolites follow Michaelis-Menten kinetics. Although these models predict the urinary metabolites formed from benzene exposures, they offer no information regarding the dosimetry of oxidative metabolites in the

bone marrow, a site of action. However, the target specificity of benzene toxicity for the bone marrow progenitor cells irrespective of route of administration is well documented in both humans and experimental animal models. Thus, route-to-route extrapolation is justified and introduces a lower degree of uncertainty than extrapolating from test animals to humans (U.S. EPA, 1999). Use of a modifying factor of 3 was considered to recognize uncertainties in the route-to-route extrapolation; however, it was deemed unnecessary. The RfD is based on human data for a sensitive endpoint; thus, it was felt that the composite UF of 300 provides sufficient protection.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 2002

This assessment was peer reviewed by external scientists as well as in response to public comments. Their comments have been evaluated carefully and incorporated in the finalization of this IRIS Summary. The **peer review document** (12 pages, 135 Kbytes) is available in Adobe PDF format.

Other EPA Documentation — U.S. EPA, 1985, 1999

Date of Agency Consensus — January 23, 2002

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Benzene
CASRN — 71-43-2
Last Revised — 04/17/2003

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Decreased lymphocyte count (Human occupational inhalation study of Rothman et al., 1996)	BMCL = 8.2 mg/m^3	300	1	3×10^{-2} mg/m^3

*Conversion factors: MW = 78.11. BMCL = 7.2 ppm, 8-hour TWA. Assuming 25ºC and 760 mm Hg, BMCL (mg/m^3) = 7.2 ppm x MW/24.45 = 23.0 mg/m^3. $BMCL_{ADJ}$ = 23.0 mg/m^3 x 10 $m^3/20$ m^3 x 5 days/7days = 8.2 mg/m^3. (The BMC was based on a benchmark response of one standard deviation change from the control mean.)

I.B.2. Principal and Supporting Studies (Inhalation RfC)

The RfC is based on BMD modeling of the ALC data from the occupational epidemiologic study of Rothman et al. (1996), in which workers were exposed to benzene by inhalation. A comparison analysis based on BMD modeling of hematological data from the Ward et al. (1985) subchronic experimental animal inhalation study was also conducted. In addition, comparison analyses using the LOAEL from the Rothman et al. (1996) study and the NOAEL from the Ward et al. (1985) study were performed.

Rothman et al. (1996) conducted a cross-sectional study of 44 workers exposed to a range of benzene concentrations and 44 age- and gender-matched unexposed controls, all from Shanghai, China. Twenty-one of the 44 subjects in the exposed and control groups were female. The exposed workers were from three workplaces where benzene was used–a factory that manufactured rubber padding for printing presses, a factory that manufactured adhesive tape, and a factory that used benzene-based paint. The unexposed workers were from two workplaces: a factory that manufactured sewing machines and an administrative facility. Workers who had a prior history of cancer, therapeutic radiation, chemotherapy, or current pregnancy were excluded. Requirements for inclusion in the study were current employment for at least 6 months in a factory that used benzene, minimal exposure to other aromatic solvents, and no exposure to other chemicals known to be toxic to bone marrow or to ionizing radiation. Controls who had no history of occupational exposure to benzene or other bone marrow-toxic agents were frequency-matched to the exposed subjects on age (5-year intervals) and gender.

Benzene exposure was monitored by organic vapor passive dosimetry badges worn by each worker for a full workshift on 5 days within a 1-2 week period prior to collection of blood samples. Benzene exposure of controls in the sewing machine factory was monitored for 1 day, but no exposure monitoring was performed in the administrative facility. Benzene exposure was also evaluated by analyzing for benzene metabolites in urine samples collected at the end of the benzene exposure period for the exposed subjects. Historical benzene exposure of the subjects was evaluated by examining employment history. Data on age, gender, current and lifelong tobacco use, alcohol consumption, medical history, and occupational history were collected by interview. Six hematological measurements were evaluated: total WBC count, ALC, hematocrit, RBC count, platelet count, and MCV. Total WBC counts and ALC were performed using a Coulter T540 blood counter. Abnormal counts were confirmed. Benzene metabolites in urine were measured by an isotope dilution gas chromatography/mass spectometry assay. Correlation analyses were performed with Spearman rank order correlation. The Wilcoxon rank sum test was used to test for hematological differences.

Mean (standard deviation) years of occupational exposure to benzene were 6.3 (4.4) with a range of 0.7-16 years. The median 8-hour TWA benzene exposure concentration for all exposed workers was 31 ppm (99 mg/m^3). Exposure to toluene and xylene was <= 0.2 ppm (0.6 mg/m^3) in all groups. The exposed group was subdivided into two equal groups of 22-one group comprising workers who were exposed to greater than the median concentration and the other containing those exposed to less than the median concentration. The median (range) 8-hour TWA exposure concentration was 13.6 (1.6-30.6) ppm (43.4 [5.1-97.8] mg/m^3] for the low-exposure group and 91.9 (31.5-328.5) ppm (294 [101-1049] mg/m^3) for the high-exposure group. A subgroup of the low-exposure group composed of 11 individuals who were not

exposed to >31 ppm (100 mg/m^3) at any time during the monitoring period was also examined in some comparisons. The median (range) 8-hour TWA exposure of these individuals was 7.6 (1-20) ppm (24 [3.2-64] mg/m^3). The urinary concentrations of the metabolites phenol, muconic acid, hydroquinone, and catechol were all significantly correlated with measured benzene exposure.

All six blood parameters measured were significantly different in the high-benzene exposure group as compared to controls. ALC, WBC count, RBC count, hematocrit, and platelets were all significantly decreased, and MCV was significantly increased. The ALC was reduced from 1.9 x 10^3/µL blood in controls to 1.6 x 10^3/µL (p<0.01) in the <31 ppm (99 mg/m^3) group and to 1.3 x 10^3/µL (p<0.001) in the group exposed to >31 ppm benzene. In the subgroup of 11 workers exposed to a median 8-hour TWA of 7.6 ppm (24 mg/m^3) benzene, the ALC (1.6 x 10^3/µL) was also significantly reduced (p=0.03). The RBC and platelet counts were also significantly reduced in the <31 ppm exposure group, but only ALC was significantly different in the low-exposure subgroup. The fact that no other measured blood cell parameters were significantly different in this subgroup suggests that ALC was the most sensitive measure of benzene hematotoxicity and that this exposure level (median 8-hour TWA of 7.6 ppm) may be at the low end of the range of benzene exposures eliciting hematotoxic effects in humans.

ALC is also thought to have a potential role as a "sentinel" effect for a cascade of early hematological and related biological changes that might be expected to result in the more profound examples of benzene poisoning observed in other cohorts of the National Cancer Institute/Chinese Academy of Preventive Medicine study, as described by Dosemeci et al. (1996). That ALC depletion is accompanied by gene-duplicating mutations in somatic cells under the same range of exposure conditions suggests that benzene can cause repeated damage to longer-lived stem cells in human bone marrow, further implicating the compound as etiologically important in the onset of benzene-associated leukemia. This finding underlines the importance of basing public health concern for benzene on a toxicological effect that is representative of the earliest biological changes induced by the compound.

BMD modeling of the ALC exposure-response data from Rothman et al. (1996) was done using U.S. EPA's Benchmark Dose Modeling Software (version 1.20). The data are rather supralinear, that is, the change in ALC per unit change in exposure decreases with increasing exposure; therefore, in order to fit the data with one of the available continuous models, the exposure levels were first transformed according to the equation d' = ln(d+1). Then the exposure-response data were fitted using the continuous linear model, which provided a good fit (p=0.54). A two-degree polynomial and a power model also fit the data, but the linear model was selected because it is the most parsimonious. The parameters were estimated using the method of maximum likelihood. A constant variance model was used.

In the absence of a clear definition for an adverse effect for this continuous endpoint, a default benchmark response of one standard deviation change from the control mean was selected, as suggested in EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000). This default definition of a benchmark response for continuous endpoints corresponds to an excess risk of approximately 10% for the proportion of individuals below the 2nd percentile (or above the 98th percentile) of the control distribution for normally distributed effects (see U.S. EPA, 2000). A 95% lower confidence limit (BMCL) on the resulting BMC was calculated using the likelihood profile method. Transforming the results back to the original exposure scale yields a BMC of 13.7 ppm (8-hr TWA) and a BMCL of 7.2 ppm (8-hr TWA).

As suggested in the draft technical guidance document (U.S. EPA, 2000), the BMCL is chosen as the point of departure for the RfC derivation. An adjusted BMCL is calculated by converting ppm to mg/m^3 and adjusting the 8-hour TWA occupational exposure to an equivalent continuous environmental exposure. The BMCL is first converted to mg/m^3 using the molecular weight of 78.11 for benzene and assuming 25ºC and 760 mm Hg: 7.2 ppm x 78.11/24.45 = 23.0 mg/m^3. The converted value is then adjusted from the 8-hour occupational TWA to a continuous exposure concentration using the default respiration rates (U.S. EPA, 1994): $BMCL_{ADJ}$ = 23.0 mg/m^3 x (10 m^3/20 m^3) x 5 days/7 days = 8.2 mg/m^3.

The RfC is then derived by dividing the adjusted BMCL by the overall UF of 300: RfC = $BMCL_{ADJ}$/UF = 8.2 mg/m^3 ÷ 300 = 3 x 10^{-2} mg/m^3. The overall UF of 300 comprises a UF of 3 for effect-level extrapolation, 10 for intraspecies differences (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies (see Section I.B.3).

For comparison, an RfC was also calculated based on the LOAEL of 7.6 ppm (8-hr TWA) from the Rothman et al. (1996) study. Converting the units and adjusting for continuous exposure as above results in a $LOAEL_{ADJ}$ of 8.7 mg/m^3. The $LOAEL_{ADJ}$ is then divided by an overall UF of 1000 to obtain the RfC: 8.7 mg/m^3 ÷ 1000 = 9 x 10^{-3} mg/m^3. The combined UF of 1000 represents UFs of 10 to account for the use of a LOAEL because of the lack of an appropriate NOAEL, 10 for intraspecies differences in response (human variability), 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies. The value of 9 x 10^{-3} mg/m^3 is in good agreement with the RfC of 3 x 10^{-2} mg/m^3 calculated from the BMC.

A comparison RfC derivation based on BMD modeling of hematological data from the Ward et al. (1985) subchronic experimental animal inhalation study was also conducted. The Ward study was selected because it used a relatively long inhalation exposure duration and an adequate number of animals, and it provided dose-response data. Ward et al. exposed male and female CD-1 mice and Sprague-Dawley rats to 0, 1, 10, 30 or 300 ppm (0, 3.2, 32, 96 or 960 mg/m^3) benzene, 6 hours/day, 5 days/week for 91 days and measured various hematological endpoints. The study identified both a LOAEL of 300 ppm and a NOAEL of 30

ppm. The male mouse appeared to be the most sensitive sex/species in this study. The exposure-response relationships for the different hematological endpoints for the male mouse were modeled using a BMD modeling approach and decreased hematocrit (i.e., volume percentage of erythrocytes in whole blood) was chosen as the critical effect.

U.S. EPA's Benchmark Dose Modeling Software (version 1.20) was used for the modeling. An assumption of constant variance was used, although the test for homogeneity of the variances failed. The continuous linear, polynomial, and power models all resulted in the same BMC and BMCL estimates; however, the linear model had better results for the fit statistics. The linear model had a p-value of 0.09, which is of borderline adequacy (the draft technical guidance document [U.S. EPA, 2000] recommends a p-value of >= 0.1), and the other models had p-values of 0.04. Thus the continuous linear model was selected. The parameters were estimated using the method of maximum likelihood.

In the absence of a clear definition for an adverse effect for this continuous endpoint, a default benchmark response of one standard deviation from the control mean was selected, as suggested in the draft technical guidance document (U.S. EPA, 2000). The software uses the estimated standard deviation. A 95% lower confidence limit (BMCL) on the resulting BMC was calculated using the likelihood profile method. A BMC of 100.7 ppm and a BMCL of 85.0 ppm were obtained.

It should be noted that the dose spacing in this study was less than ideal. Responses in the three lower exposure groups for all the hematological endpoints tended to clump near control group levels, and significant deviations in response were generally seen only in the 300 ppm group, with a large exposure range in between, including where the BMC is located, for which there are no response data. Therefore, there is some uncertainty about the actual shape of the exposure-response curve in the region of the benchmark response and, thus, some corresponding uncertainty about the values of the BMC and BMCL estimates.

ALCs were not reported in Ward et al. (1985), so this endpoint could not be compared to the human ALC results. Total WBC counts were reported and exhibited the largest percent change in response between the control and the 300 ppm group; however, the data for this endpoint also had substantial variance, and because the benchmark response used for this analysis is a function of the standard deviation, WBC count did not yield the lowest BMC estimate. The actual lowest BMC estimates were obtained for increased mean cell hemoglobin (MCH) (78 ppm; BMCL = 67 ppm) and increased mean cell volume (79 ppm; BMCL = 68 ppm); however, these endpoints are probably not adverse per se. On the other hand, they are likely to be compensatory effects and, thus, markers of toxicity, and one could probably justify using them as the critical effects. In any event, the BMC estimates are not much different from the BMC of 100 ppm obtained for decreased hematocrit. The results are also similar for total

blood hemoglobin (BMC = 104 ppm, BMCL = 88 ppm). RBC count results were in between those for MCV and MCH and those for hematocrit and total hemoglobin; however, the model fits were not adequate for the RBC data and, thus, the RBC results have more uncertainty.

To derive the RfC, the BMCL is used as the point of departure, as suggested in the draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000). For conversion of the inhalation exposures across species, ppm equivalence was assumed; this is identical to using EPA's inhalation dosimetry methodology with Regional Gas Dose Ratio for the respiratory tract region ($RGDR_r$) = 1 (U.S. EPA, 1994). The BMCL is first converted to mg/m^3 using the molecular weight of 78.11 for benzene and assuming 25ºC and 760 mm Hg: BMCL (mg/m^3) = 85.0 ppm x 78.11/24.45 = 272 mg/m^3. The converted value is then adjusted to an equivalent continuous exposure: $BMCL_{ADJ}$ = 272 mg/m^3 x (6 hrs/24 hrs) x 5 days/7 days = 48.5 mg/m^3.

The RfC is then obtained by dividing the adjusted BMCL by the overall UF of 1000: RfC = 48.5 $mg/m^3 \div 1000 = 5 \times 10^{-2}$ mg/m^3. The overall UF of 1000 comprises a UF of 3 for effect-level extrapolation, 3 for interspecies extrapolation (inhalation), 10 for intraspecies differences, 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies (see Section I.B.3). This value is in good agreement with the RfC of 3×10^{-2} mg/m^3 calculated from the BMC from the Rothman et al. (1996) human study.

For further comparison, an RfC was also calculated, based on the NOAEL of 30 ppm from the Ward et al. (1985) study. Converting the units and adjusting for continuous exposure as above results in a $NOAEL_{ADJ}$ of 17.1 mg/m^3. The $NOAEL_{ADJ}$ is then divided by an overall UF of 300 to obtain the RfC: 17.1 $mg/m^3 \div 300 = 6 \times 10^{-2}$ mg/m^3. The combined UF of 300 represents a UF of 3 for interspecies extrapolation (inhalation), 10 for intraspecies differences, 3 for subchronic-to-chronic extrapolation, and 3 for database deficiencies. The value of 6×10^{-2} mg/m^3 is also in good agreement with the RfC of 3×10^{-2} mg/m^3 calculated from the BMC from the Rothman et al. (1996) human study.

It should be noted, however, that other experimental animal studies have reported significant hematological effects at benzene exposures of 10-25 ppm, which are lower than the NOAEL of 30 ppm from the Ward et al. (1985) study. These studies have insufficient data for dose-response modeling, and they used shorter exposure durations and/or fewer experimental animals than did the Ward et al. (1985) study; nonetheless, they observed statistically significant hematological effects at 10–25 ppm. Baarson et al. (1984), for example, exposed male C57BL/6J mice (five/group) to 10 ppm benzene, 6 hours/day, 5 days/week, for 178 days and observed statistically significant reductions in blood lymphocytes at each of the three monitoring time points (32, 66, and 178 days) when compared to controls. The magnitude of the reduction in lymphocytes ranged from about 53% at 32 days to about 68% at 178 days. Cronkite et al. (1985) exposed male and female C57BL/6 BNL mice to various concentrations

of benzene 6 hours/day, 5 days/week for 2 weeks and observed no decrease in blood lymphocytes at 10 ppm, but they did observe a statistically significant reduction of about 21% at 25 ppm as compared to controls (5–10 mice/group). Thus, lower RfCs than those calculated above for the Ward et al. (1985) study are possible, based on other experimental animal results. In the most extreme case, using a LOAEL of 10 ppm and an overall UF of 3000 yields a $LOAEL_{ADJ}$ of 5.7 mg/m^3 and an RfC of 2 x 10^{-3} mg/m^3.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 300 for the BMCL from the Rothman et al. (1996) study.

First, because the BMC is considered to be an adverse effect level, an effect level extrapolation factor analogous to the LOAEL-to-NOAEL UF is used. U.S. EPA is planning to develop guidance for applying an effect level extrapolation factor to a BMD. In the interim, a factor of 3 will be used in this analysis (see Section I.A.3). For a more serious effect, a larger factor, such as 10, might be selected. Second, a factor of 10 was used for intraspecies differences in response (human variability) as a means of protecting potentially sensitive human subpopulations. Third, a UF of 3 for subchronic-to-chronic extrapolation was applied (see Section I.A.3). Finally, a UF of 3 was chosen to account for database deficiencies, because no two-generation reproductive and developmental toxicity studies for benzene are available. Therefore, an overall UF of 3 x 10 x 3 x 3 = 300 is used to calculate the RfC.

For the comparison analysis based on the Rothman et al. (1996) LOAEL, the following UFs were selected: a factor of 10 for use of a LOAEL due to lack of an appropriate NOAEL, a factor of 10 for intraspecies variability, a factor of 3 for subchronic-to-chronic extrapolation, and a factor of 3 for database deficiencies. Hence, an overall UF of 10 x 10 x 3 x 3 = 1000 was used in the comparison analysis.

For the comparison analysis based on the BMCL calculated from BMD modeling of the male mouse data from the Ward et al. (1985) subchronic inhalation study, the following UFs were used: a UF of 3 for effect-level extrapolation, which is analogous to the LOAEL-to-NOAEL extrapolation factor, because the BMC is considered an adverse effect level; a UF of 3 for interspecies extrapolation for inhalation studies; a UF of 10 for intraspecies variability; and a UF of 3 for database deficiencies. In addition, a partial UF of 3 was used to extrapolate from subchronic to chronic exposure. This partial value was selected based on the observation that hematological fluctuations such as reductions in RBCs and WBCs in the high-dose mice were noted at interim sacrifice (14 days) as well as at termination (91 days), suggesting that the responses occurred early in the exposure cycle and then remained comparatively unchanged. Thus, an overall UF of 3 x 3 x 10 x 3 x 3 = 1000 was used in this comparison analysis.

Finally, for the comparison analysis based on the NOAEL from the Ward et al. (1985) subchronic inhalation study, the following UFs were used: 3 for interspecies extrapolation for inhalation studies, 10 for intraspecies variability, 3 for database deficiencies, and 3 for subchronic-to-chronic extrapolation, as above. Therefore, an overall UF of 300 was used in this comparison analysis.

MF = None. No modifying factor was considered necessary.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Benzene is toxic by all routes of administration. Hematotoxicity and immunotoxicity have been consistently reported to be the most sensitive indicators of noncancer toxicity in both humans and experimental animals, and these effects have been the subject of several reviews (Aksoy, 1989; Goldstein, 1988, Snyder et al., 1993; Ross, 1996; U.S. EPA, 2002). The bone marrow is the target organ for the expression of benzene hematotoxicity and immunotoxicity. Neither gastrointestinal effects from oral exposure nor pulmonary effects due to inhalation exposure have been reported.

Chronic exposure to benzene results in progressive deterioration in hematopoietic function. Anemia, leukopenia, lymphocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported after chronic benzene exposure (Aksoy, 1989; Goldstein, 1988). In an earlier follow-up study of benzene-exposed workers, Aksoy et al. (1972) reported that 8 of 32 workers who had been diagnosed with pancytopenia died, mainly from infection and bleeding. In contrast to these blood cellularity depression effects, benzene is also known to induce bone marrow hyperplasia. Acute myelogenous leukemia has been frequently observed in studies of human cohorts exposed to benzene, and there is evidence linking benzene exposure to several other forms of leukemia. Whether the hematotoxic/immunotoxic effects of benzene exposure and its carcinogenic effects are due to a common mechanism is not yet known. This is in part due to the fact that although the bone marrow depressive effects of exposure to benzene in humans can be readily duplicated in several experimental animal model systems, a suitable experimental animal system for the induction of leukemia has not been found. The hematotoxicity/immunotoxicity effects of benzene exposure lead to significant health effects apart from potential induction of leukemia, as several deaths due to aplastic anemia have been reported (ATSDR, 1997).

Leukocytopenia has been consistently shown to be a more sensitive indicator of benzene toxicity in experimental animal systems than anemia, and lymphocytopenia has been shown to be an even more sensitive indicator of benzene toxicity than overall leukocytopenia (Snyder et al., 1980, Ward et al., 1985; Baarson et al., 1984). Rothman et al. (1996) also found that a decrease in ALC was the most sensitive indicator of benzene exposure in a group of workers.

Ward et al. (1996) observed a strong relationship between benzene exposure and decreased WBC counts in a rubber worker cohort, but no significant relationship with RBC counts was found.

Bogardi-Sare et al. (2000) found that exposure to benzene concentrations of less than 15 ppm can induce depression of circulating B-lymphocytes. Dosemeci et al. (1996) were able to demonstrate the presence of benzene poisoning (WBC <4000 cells/mm^3 and platelet count <80,000/mm^3) at levels of exposure in the 5–19 ppm range.

As is the case with many other organic solvents, benzene has been shown to produce neurotoxic effects in test animals and humans after short-term exposures to relatively high concentrations (U.S. EPA, 2002). The neurotoxicity of benzene, however, has not been extensively studied, and no systematic studies of the neurotoxic effects of long-term exposure have been conducted. Additionally, there is some evidence from human epidemiologic studies of reproductive and developmental toxicity of benzene, but the data did not provide conclusive evidence of a link between exposure and effects (U.S. EPA, 2002). Some test animal studies provide limited evidence that exposure to benzene affects reproductive organs; however, these effects were limited to high exposure concentrations that exceeded the maximum tolerated dose (U.S. EPA, 2002). Results of inhalation studies conducted in test animals are fairly consistent across species and have demonstrated that at concentrations of greater than 150 mg/m^3 (47 ppm) benzene is fetotoxic and causes decreased fetal weight and/or minor skeletal variants (U.S. EPA, 2002). Exposure of mice to benzene in utero has also been shown to cause changes in the hematogenic progenitor cells in fetuses, 2-day neonates, and 6 week-old adults (Keller and Snyder, 1986, 1988).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.4 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

The overall confidence in this RfC assessment is medium. The principal study of Rothman et al. (1996) was well conducted, and the availability of good-quality human data for a sensitive endpoint eliminates the uncertainty associated with basing the RfC on experimental animal data. In addition, the RfC of 3×10^{-2} mg/m^3 obtained from the BMD modeling results from the Rothman et al. (1996) study is in good agreement with the value of 9×10^{-3} mg/m^3 based on the LOAEL. The RfC is also in good agreement with the values of 5×10^{-2} mg/m^3 and 6×10^{-2}

mg/m^3 based on the BMC and the NOAEL, respectively, from the Ward et al. (1985) subchronic rodent inhalation study. This consistency in results provides increased confidence in the RfC.

With continuous endpoints such as hematological parameters, there is uncertainty about when a change in a parameter that has inherent variability becomes an adverse effect. Other uncertainties explicitly recognized in the quantitative derivation include intraspecies variability (to accommodate sensitive human subgroups), subchronic-to-chronic extrapolation, and database deficiencies due to the lack of two-generation reproductive and well-conducted developmental toxicity studies for benzene.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2002.

This assessment was peer reviewed by external scientists as well as in response to public comments. Their comments have been evaluated carefully and incorporated in the finalization of this IRIS Summary. The **peer review document** (12 pages, 135 Kbytes) is available in Adobe PDF format.

Other EPA Documentation — None

Date of Agency Consensus — January 23, 2002

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Benzene
CASRN — 71-43-2
Last Revised — 01/19/2000

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Benzene is classified as a "known" human carcinogen (Category A) under the Risk Assessment Guidelines of 1986. Under the proposed revised Carcinogen Risk Assessment Guidelines (U.S. EPA, 1996), benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies. (U.S. EPA, 1979, 1985, 1998; ATSDR, 1997).

Epidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and acute nonlymphocytic leukemia (ANLL) and also suggest evidence for chronic nonlymphocytic leukemia (CNLL) and chronic lymphocytic leukemia (CLL). Other neoplastic conditions that are associated with an increased risk in humans are hematologic neoplasms, blood disorders such as preleukemia and aplastic anemia, Hodgkin's lymphoma, and myelodysplastic syndrome (MDS). These human data are supported by animal studies. The experimental animal data add to the argument that exposure to benzene increases the risk of cancer in multiple species at multiple organ sites (hematopoietic, oral and nasal, liver, forestomach, preputial gland, lung, ovary, and mammary gland). It is likely that these

responses are due to interactions of the metabolites of benzene with DNA (Ross, 1996; Latriano et al., 1986). Recent evidence supports the viewpoint that there are likely multiple mechanistic pathways leading to cancer and, in particular, to leukemogenesis from exposure to benzene (Smith, 1996).

II.A.2. Human Carcinogenicity Data

Benzene is a known human carcinogen based upon evidence presented in numerous occupational epidemiological studies. Significantly increased risks of leukemia, chiefly acute myelogenous leukemia (AML), have been reported in benzene-exposed workers in the chemical industry, shoemaking, and oil refineries.

The following epidemiologic studies briefly described are the key studies that support the weight-of-evidence classification that exposure to benzene is causally related to an increase in the risk of cancer, specifically leukemia.

Aksoy et al. (1974) reported effects of benzene exposure among 28,500 Turkish workers employed in the shoe industry. The mean duration of employment was 9.7 years (range 1 to 15 years) and the mean age was 34.2 years. Peak exposure to benzene was reported to be 210 to 650 ppm. Twenty-six cases of leukemia and a total of 34 leukemias or preleukemias were observed, corresponding to an incidence of 13/100,000 (by comparison to 6/100,000 for the general population). A follow-up analysis of the study (Aksoy, 1980) reported eight additional cases of leukemia as well as evidence suggestive of increases in other malignancies. This case study lacks detailed information on personal exposure to benzene and potential exposure to other chemicals, a well-defined comparison population, and control of confounding variables.

Infante et al. (1977b), in a retrospective cohort mortality study, examined the leukemogenic effects of benzene exposure in 748 white male workers exposed at least 1 day while employed in the manufacture of rubber products. Exposure occurred from 1940 to 1949 and vital status was obtained through 1975. A statistically significant increased risk of leukemia (7 observed, 1.48 expected; $p < .002$) was found by comparison of observed leukemia deaths in this cohort with those expected based upon general U.S. population death rates. The risk of leukemia was said by the authors to be potentially understated since follow-up was only 75% complete. According to the authors, there was no evidence of solvent exposure other than benzene. No effort was made to evaluate individual exposures to benzene for the purpose of doing a dose-response analysis. The main criticism of this study, as well as its later updates, is the small size of the cohort.

In an extension and elaboration of the analysis done by Infante et al. (1977b), Rinsky et al. (1981) reported seven deaths from leukemia in this same cohort after achieving a 98% vital

status ascertainment through June 1975. Forty additional deaths from all causes were reported, but no new leukemia deaths. Again, the risk of death from leukemia was statistically significant (standardized mortality ratio [SMR] was 560 based upon 7 leukemia deaths, $p < .001$). Some 437 members of the cohort were exposed for less than 1 year. Those who received 5 or more years of exposure exhibited an SMR of 2100, based upon 5 leukemia deaths versus 0.25 expected ($p < .01$). All seven leukemia cases were of the myelogenous or monocytic cell type. Four additional deaths from leukemia were also noted but could not be added to the total because they did not fit the criteria for inclusion. The authors tried to reconstruct past exposure to benzene at the two locations of this company and found that in some areas of the plants airborne benzene concentrations occasionally rose to several hundred parts per million, but most often employee 8-hour time-weighted averages (TWA) fell within the limits considered permissible at the time of exposure. No dose-response analysis was attempted.

In an updated version of the Rinsky et al. (1981) study, the same authors examined a somewhat expanded cohort of 1165 nonsalaried white men employed in the rubber hydrochloride department for at least 1 day through December 1965 and followed to December 31, 1981 (Rinsky et al., 1987). Followup was 98.6% complete. Again, a statistically significant excess risk of leukemia was found for the total cohort (9 observed, 2.7 expected; $p < 0.05$). For the first time, individual measurements of cumulative exposure in terms of ppm-years were generated for all members of the cohort utilizing the historical air-sampling data discussed above or interpolating estimates based on the existing data. SMRs for leukemia ranged from a nonsignificant 109 (2 observed, 1.83 expected) at cumulative exposures under 40 ppm-years to a statistically significant SMR of 2339 (5 observed, 0.21 expected; $p < .05$) at 200 ppm-years or more of exposure. The authors found significantly elevated risks of leukemia at cumulative exposures less than the then equivalent current standard for occupational exposure, which was 10 ppm over a 40-year working lifetime.

The Rinsky et al. (1981, 1987) study analyses, based upon the original cohort of Pliofilm rubber workers studied by Infante et al. (1977b), were selected by the Agency as the critical study for dose-response analysis and for the quantitative estimation of cancer risk to humans. The Rinsky et al. (1981, 1987) analyses show ample power, latency, reasonably good estimates of exposure to benzene except prior to 1946, few confounders, and a wide range of exposure to benzene from low levels to high levels. Limitations include the small cohort size, reporting only nine leukemia deaths with no estimates of risk according to cell type. There remain questions about the estimation of personal exposure to benzene, especially prior to 1946 when no measurements of airborne benzene were made. And finally, at levels less than 200 ppm-years it is not possible to determine leukemia risk in this cohort because of lack of sensitivity of the data at low levels.

Ott et al. (1978) observed a nonsignificantly increased risk of leukemia (3 deaths) among 594 chemical workers exposed to benzene followed for at least 23 years in a retrospective cohort mortality study. Benzene exposures ranged from under 2 ppm to over 25 ppm 8-hour TWA. Bond et al. (1986) updated this report by following this cohort an additional 9 years to the end of 1982 and adding an additional 362 exposed workers not studied previously. The authors reported finding a nonsignificant excess risk (SMR = 194) of deaths from leukemia based upon 4 cases. All were diagnosed as myelogenous leukemias. The authors reported that this represented a significant excess (4 observed versus 0.9 expected, $p < .011$) for myelogenous leukemia based upon the International Classification of Diseases and Causes of Death. It is not stated whether these four deaths were acute or chronic. One additional death was classified as a "pneumonia" death, but on the death certificate "acute myelogenous leukemia" was noted as a significant contributing condition. Cumulative exposure estimates ranged from 18 ppm-months to a high of 4211 ppm-months. The Bond et al. (1986) study has little power to detect significant risk of leukemia at low doses. The authors also state that their data should not be used for determining unit risk estimates because of the small number of events, competing exposures to other potentially hazardous materials, and the contribution of unquantified brief exposures to benzene.

Wong (1983, 1987) reported on the mortality of male chemical workers who had been exposed to benzene for at least 6 months during the years 1946 to 1975. The study population of 4602 persons was drawn from seven chemical plants and cumulative exposures to benzene were determined for all subjects. The control subjects (3074 persons) held jobs at the same plants for at least 6 months but were never subjected to benzene exposure. Dose-dependent increases were seen in the risk of leukemia and the risk of lymphatic and hematopoietic cancer. Chemical workers with a cumulative exposure to benzene of 720 ppm-months were subject to a borderline significant relative risk of 3.93 ($p = .05$) for lymphatic and hematopoietic cancer. None of the leukemia deaths were of the acute myeloid cell type, the type that was known to be associated with exposure to benzene in other studies. The author further observed that cumulative exposure, not peak exposure, was the major variable in quantifying mortality risk from lymphopoietic cancer. The Mantel-Haenszel chi-square for upward trend in risk of leukemia with increasing cumulative exposure was significantly elevated at the 99% level of confidence. Some of the limitations of this study include imprecise historical industrial hygiene data, unusual distribution of leukemia cell types, i.e., there were no acute cases of myelogenous leukemia out of seven leukemia cases, and possible exposure of comparison subjects to potentially carcinogenic solvents other than benzene.

The National Cancer Institute of the U.S. National Institutes of Health and the Chinese Academy of Preventative Medicine have been conducting a comprehensive epidemiological study of 74,828 benzene-exposed workers employed from 1972 to 1987 in 672 factories in 12 cities of China (Dosemeci et al., 1994; Hayes et al., 1996, 1997; Yin et al., 1987, 1989, 1994,

1996). A comparison group of workers consisting of 35,805 employees was assembled from non-benzene-exposed units of 69 of the same factories and 40 factories elsewhere. Workers in a variety of jobs in painting, printing, footwear, rubber, chemical, and other industries were followed for vital status for an average period of time of less than 12 years. Less than 0.3% were lost to follow-up. Employee work histories were linked to benzene exposure data in order to derive individual time-specific estimates for each worker (Dosemeci et al., 1994). This large cohort mortality study produced a significantly elevated risk of hematologic neoplasms (RR = 2.2, 95% C.I. = 1.1-4.2) in workers exposed to benzene at an average level of less than 10 ppm. A combination of ANLL and MDS produced a risk of 3.2 (95% C.I .= 1.0-10.1). For exposure to a sustained concentration of 25 ppm benzene, the risk of ANLL and MDS increased to 7.1 (95% C.I. = 2.1-23.7). The risk of other leukemias (other than ANLL), including chronic myeloid and monocytic leukemia, was not significantly elevated (RR = 2.0). Additionally, the risk of non-Hodgkin's lymphoma was significantly elevated (RR = 4.2 with 95% C.I. = 1.1-15.9) for those with a sustained exposure to benzene that occurred at least 10 years prior to diagnosis. The authors concluded that benzene exposure "is associated with a spectrum of hematologic neoplasms and related disorders in humans and that risks for these conditions are elevated at average benzene-exposure levels of less than 10 ppm." Limitations of this study include possible concurrent exposures to many different chemicals found in the factories where the benzene exposure occurred. There is a lack of reliable exposure information in the early days of the observation period, when only 3% of the exposure estimates were based on actual measurements.

All of the epidemiological studies referred to above have some methodological problems, i.e., confounding exposures, lack of sufficient power, and other limitations, but the consistent excess risk of leukemia across all of these studies argues that such problems could not be entirely responsible for the elevated risks of cancer. Most of these epidemiologic and case studies have been reviewed in peer-reviewed publications (IARC, 1982; ATSDR, 1997; U.S. EPA, 1998). They provide clear evidence of a causal association between exposure to benzene and ANLL. The evidence is suggestive with respect to CNLL and CLL.

The limitations of these studies, except for Rinsky et al. (1981, 1987), preclude their use in quantitative risk estimation. This is further discussed in the quantitative risk estimation sections (II.C.3 and II.C.4).

II.A.3. Animal Carcinogenicity Data

Although human epidemiological studies provide the bulk of the evidence reaffirming the classification of benzene as a category A, "known" human carcinogen (U.S. EPA, 1979, 1985, 1998), many experimental animal studies, both inhalation and oral, also support the evidence that exposure to benzene increases the risk of cancer in multiple organ systems including the

hematopoietic system, oral and nasal cavities, liver, forestomach, preputial gland, lung, ovary, and mammary gland. The key animal studies that support the finding of an excess risk of leukemia in humans from exposure to benzene by the inhalation route are Maltoni et al. (1982, 1983, 1985, 1989), Cronkite et al. (1984, 1985, 1989), Snyder et al. (1988), and Farris et al. (1993); and by the oral route, Huff et al. (1989), NTP (1986), and Maltoni et al. (1983, 1985, 1989). The details of these studies have been reviewed (ATSDR, 1997). Studies on the carcinogenicity of benzene in rodents include inhalation exposures to Sprague-Dawley rats, C57BL/6 mice, AKR mice, CD-1 mice, and CBA mice; and gavage treatment of Sprague-Dawley rats, Wistar rats, F344 rats, RF/J mice, Swiss mice, and B6C3F1 mice (Cronkite et al., 1989; Goldstein et al., 1982; Huff et al., 1989; Maltoni et al., 1983, 1988; NTP, 1986; Snyder et al., 1980, 1982, 1984; Farris et al., 1993). Inhalation concentrations ranged from 0 to 1000 ppm and gavage doses ranged from 0 to 200 mg/kg.

It is noted that in humans the cancer induced by benzene exposure is predominantly acute nonlymphocytic leukemia, while in rodents lymphocytic leukemia was observed in two series of experiments in C57BL/6 mice (Snyder et al., 1980) and CBA/Ca mice (Cronkite et al., 1989). The difference in induction of hematopoietic cancers in mice and humans is not fully understood, but it may be related to species-specific differences in hematopoiesis. Lymphocytes make up a larger portion of the nucleated cells in mouse bone marrow than in human bone marrow (Parmley, 1988) and could simply represent a larger target cell population for benzene metabolites. The bone marrow, Zymbal gland, and Harderian gland all contain peroxidases, which can activate phenols to toxic quinones and free radicals. Sulfatases, which remove conjugated sulfate and thus reform free phenols, are also present at high levels in these target organs. The selective distribution of these two types of enzymes in the body may explain the accumulation of free phenol, hydroquinone, and catechol in the bone marrow and the resulting differences in target organ toxicity of benzene metabolites in humans and animals. The animal bioassay results may have some relevance to human leukemia, but it should be emphasized that there is no well-demonstrated and reproducible animal model for leukemia resulting from benzene exposure. The mechanism of leukemia development following exposure to benzene is not well understood (Low et al., 1989, 1995).

II.A.4. Supporting Data for Carcinogenicity

The supporting evidence for the carcinogenic effects of exposure to benzene comes from our current understanding of the metabolism and mode of action (Stephens et al., 1994; Medinsky et al., 1996; Lee et al., 1996; Valentine et al., 1996; Rothman, 1997). This is briefly summarized below and reviewed in U.S. EPA (1998).

It is generally agreed that the toxicity of inhaled benzene results from its biotransformation to reactive species. Benzene is metabolized in the liver by cytochrome P4502E1 (CYP2E1) to its

major metabolites: phenol, hydroquinone, and catechol. The intermediate benzene oxide can also undergo ring opening to trans-trans muconic acid. Although there is a scientific consensus that metabolism of benzene is required for resultant toxicity and carcinogenic response, the role of a metabolite or metabolites of benzene in producing these adverse effects is controversial and more research data are needed to better define sequelae of pathogenesis following exposure to benzene and its metabolites. Current evidence indicates that benzene-induced myelotoxicity and genotoxicity result from a synergistic combination of phenol with hydroquinone, muconaldehyde, or catechol.

Molecular targets for the action of these metabolites, whether acting alone or in concert, include tubulin, histone proteins, topoisomerase II, and other DNA-associated proteins. Damage to these proteins would potentially cause DNA strand breakage, mitotic recombination, chromosomal translocations, and malsegregation of chromosomes to produce aneuploidy. If these effects took place in stem or early progenitor cells, a leukemic clone with selective advantage to grow could arise as a result of protooncogene activation, gene fusion, and suppressor-gene inactivation. Epigenetic effects of benzene metabolites on the bone marrow stroma, and perhaps the stem cells themselves, could then foster development and survival of a leukemic clone. Since these plausible events have not been conclusively demonstrated, this remains a hypothesis (Smith, 1996).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

II.B.1.1. Oral Slope Factor — 1.5×10^{-2} to 5.5×10^{-2} per (mg/kg)/day

II.B.1.2. Drinking Water Unit Risk — 4.4×10^{-7} to 1.6×10^{-6} per (ug/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 10^4)	10^2 µg/L to 10^3 µg/L
E-5 (1 in 10^5)	10^1 µg/L to 10^2 µg/L
E-6 (1 in 10^6)	10^0 µg/L to 10^1 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 oral absorption of benzene in humans. Inhalation absorption is assumed to be about 50% while that of oral is selected as 100% based upon a review of the relevant human and animal literature (U.S. EPA, 1999). Absorption of benzene via the dermal route of exposure is usually less than 1% of the applied dose and therefore it is not considered to contribute significantly the oral risk estimation. In the previous oral unit risk estimate it was assumed that absorption was equal for both the inhalation and oral routes of exposure (U.S. EPA, 1992). The inhalation unit risk range (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 for an adult human, 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 L/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 dated April 1, 1992.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

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 µg/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 given above, the dose from 1 µg/m^3 continuous daily exposure is:

1 µg/m^3*20 m^3/day*0.5*(1/70) kg = 0.143 µg/kg/day

The risk estimate range is then divided by this dose, to generate an oral slope factor in units of inverse dose:

risk/(µg/kg/day)	= 2.2×10^{-6}/0.143 µg/kg/day to 7.8×10^{-6}/0.143 µg/kg/day = 1.54×10^{-5} to 5.45×10^{-5} per µg/kg/day

Assuming 100% oral 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 µg/kg/day*70 kg*(2 L/day)$^{-1}$ = 35 µg/L

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

(1.54×10^{-5} to 5.45×10^{-5})/35 µg/L = 4.4×10^{-7} to 1.6×10^{-6}/µg/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).

If one assumes a 20% respiratory absorption rate, the lowest value in a group of subjects (range 20% to 50%) that was 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. The standard values (20 m^3/day, 70 kg, 2 L/day) used for the risk estimation do not necessarily account for the population variability.

The range of risk estimates of 4.4×10^{-7} to 1.6×10^{-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. This conclusion is supported by studies in humans (Pekari et al., 1992; 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.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

The most useful available human epidemiological data for evaluation of the risk of cancer from exposure to benzene comes from occupational inhalation exposure studies (Rinsky et al., 1981, 1987). There are few human data regarding oral exposure to benzene. Route-to-route extrapolation is justified because similar toxic effects are observed in animals through either the oral or inhalation route of exposure to benzene (ATSDR, 1997) and toxicokinetic data available from animal studies (Gerrity et al., 1990). Experimental 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 metabolite (Smith, 1996).

The 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). No relevant oral benzene exposure data on humans 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 several inhalation studies, EPA has judged an absorption factor of 50% to be the most scientifically sound.

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.

A substantial literature provides information on pulmonary absorption in humans. The animal study selected for this assessment 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.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

II.C.1.1. Air Unit Risk

A range of 2.2×10^{-6} to 7.8×10^{-6} is the increase in the lifetime risk of an individual who is exposed for a lifetime to 1 µg/m^3 benzene in air.

II.C.1.2. Extrapolation Method:

Low-dose linearity utilizing maximum likelihood estimates (Crump, 1992, 1994).

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	13.0 to 45.0 µg/m^3
E-5 (1 in 100,000)	1.3 to 4.5 µg/m^3
E-6 (1 in 1,000,000)	0.13 to 0.45 µg/m^3

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type — Leukemia
Test Species -- Humans
Route — Inhalation
References -- Rinsky et al., 1981, 1987; Paustenbach et al., 1993; Crump and Allen, 1984; Crump, 1992, 1994; U.S. EPA, 1998.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The Pliofilm workers of Rinsky et al. (1981, 1987) provide the best published set of data to date for evaluating human cancer risks from exposure to benzene. Compared to the published studies of Ott et al. (1978), Bond et al. (1986), and Wong (1987), this cohort has fewer reported co-exposures to other potentially carcinogenic substances in the workplace that might confound risk analysis for benzene. This cohort also provides a greater range of exposures than those of Ott et al. (1978), Bond et al. (1986), and Wong (1987). The Rinsky et al. data were used for developing the unit cancer risk by Crump (1992, 1994). Differences in the unit risk estimates, in addition to the choice of model used, stem largely from differences in the exposure estimates and the dose-response model used.

Although the ongoing Chinese cohort studies (Dosemeci et al., 1994; Hayes et al., 1996, 1997; Yin et al., 1987, 1989, 1994, 1996) provide a large data set and perhaps may provide information in the future to better characterize risk of cancer at low dose exposure, their use in the derivation of risk estimates remains problematic at present for the reasons cited in Section II.A.2.

The two most important determinants of the magnitude of the unit risk number are the choice of extrapolation model to be used to estimate risk at environmental levels of exposure and the choice of the exposure estimates to which the Pliofilm workers (Rinsky et al., 1981, 1987) were subjected. Crump (1992, 1994) presented 96 unit risk calculation analyses by considering different combinations of the following factors: (1) different disease endpoints, (2) additive or multiplicative models, (3) linear/nonlinear exposure-response relationships, (4) two different sets of exposure measurements (Crump and Allen [1984] vs. exposure estimates by Paustenbach et al. [1993]) and (5) cumulative or weighted exposure measurements. The unit risk estimates range from 8.6×10^{-5} to 2.5×10^{-2} at 1 ppm (3200 $\mu g/m^3$) of benzene air concentration (Crump, 1992, 1994).

The risk estimates would fall into the lower range if a sublinear exposure response model were found to be more plausible. However, the shape of the exposure dose-response curve cannot be considered without a better understanding of the biological mechanism(s) of benzene-induced leukemia. Understanding of the mechanisms by which exposure to benzene and its metabolites exert their toxic and carcinogenic effects remains uncertain (U.S. EPA, 1998). It is likely that more than one mechanistic pathway may be responsible for the toxicity of benzene contributing to the leukemogenic process. Not enough is known to determine the shape of the dose-response curve at environmental levels of exposure and to provide a sound scientific basis to choose any particular extrapolation model to estimate human cancer risk at low doses. In fact, recent data (Hayes et al., 1997) suggest that because genetic abnormalities appear at low exposures in humans, and the formation of toxic metabolites plateaus above 25 ppm, the dose-response curve could be supralinear below 25 ppm. Given this, EPA believes that use of a linear extrapolation model as a default approach is appropriate.

When a linear model was employed, the choice of cancer unit risk estimates narrows to a range between 7.1×10^{-3} and 2.5×10^{-2} at 1 ppm (2.2×10^{-6} to 7.8×10^{-6} at 1 $\mu g/m^3$ of benzene in air), depending on which exposure measurements were used, i.e., Crump and Allen (1984) or Paustenbach et al. (1993). The choice of these limits was dictated by the following considerations: (1) use of the (1981, 1987) Rinsky cohort, (2) use of Crump's (1992, 1994) analysis of the Crump and Allen (1984) and the Paustenbach (1992, 1993) exposure measurements. The range of risks nearly includes the 1985 EPA risk estimate of 2.6×10^{-2} at 1 ppm (8.1×10^{-6} at 1 $\mu g/m^3$). The set of risk estimates falling within this interval reflects both

the inherent uncertainties in the risk assessment of benzene and the limitations of the epidemiologic studies in determining dose-response and exposure data.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

The major conclusion of this update (U.S. EPA, 1998) is a reaffirmation within an order of magnitude of the benzene interim unit risk estimates derived in EPA's 1985 interim risk assessment (U.S. EPA, 1985), which established the probability of humans developing cancer from exposure to 1 ppm of benzene. Review of the 1985 interim risk assessment required addressing two main concerns.

The first concern was the use of the updated epidemiologic data from Rinsky et al.'s (1987) cohort of Pliofilm workers and selection of appropriate estimates of their exposure to benzene for the derivation of the unit risk estimate. Although numerous epidemiological studies demonstrate an association of exposure to benzene and increased risk of human cancer, these studies are not without methodological limitations. The Rinsky et al. (1981, 1987) study continues to provide the best available data for derivation of unit cancer risk estimates. This study had the least number of confounders and a wide range of exposure to benzene.

The second major concern was continued application of the low-dose linearity concept to the model used to generate estimates of unit risk. It was concluded that at present there is insufficient evidence to reject this concept, and a linear extrapolation was used (U.S. EPA, 1998). If one assumes that the linear extrapolation model is the appropriate model to be used, given the uncertainties outlined, then the range of suitable estimates is defined by the choice of exposure estimates selected. The lowest unit risk among linear choices is determined by the exposure estimates of Paustenbach et al. (1993) according to the calculations of Crump (1992, 1994), simply because Paustenbach's exposure estimates for the Rinsky cohort are highest. That estimate is 7.1×10^{-3} at 1 ppm (2.2×10^{-6} at 1 $\mu g/m^3$). The highest risk number is determined by Crump (1992, 1994) using the lower exposure estimates from Crump and Allen (1984), and that is 2.5×10^{-2} at 1 ppm (7.8×10^{-6} at 1 $\mu g/m^3$).

At present, the true cancer risk from exposure to benzene cannot be ascertained, even though dose-response data are used in the quantitative cancer risk analysis, because of uncertainties in the low-dose exposure scenarios and lack of clear understanding of the mode of action. A range of estimates of risk is recommended, each having equal scientific plausibility. The range estimates are maximum likelihood values (i.e., best statistical estimates) and were derived from observable dose responses using a linear extrapolation model to estimate low environmental exposure risks. The extrapolation range is on the order of 20-60 depending on what environmental level is of interest. This range is fairly low and thus does not suggest any unusual lack of plausibility about the estimates. The use of a linear model is a default public

health protective approach and an argument both for and against recognizing supra- and sublinear relationships at low doses and nonthreshold or threshold modes of action on exposure to benzene. Therefore, the true risk could be either higher or lower. The numerical difference between the 1985 risk estimate (2.6×10^{-2} at 1 ppm or 8.1×10^{-6} at 1 µg/m^3) compared to the new high-end risk (2.5×10^{-2} at 1 ppm or 7.8×10^{-6} at 1 µg/m^3) is insignificant and no scientific inferences about the merit of one value versus the other should be made.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Documents -- U.S. EPA, 1999; U.S. EPA, 1998; U.S. EPA, 1985; U.S. EPA, 1979.

The U.S. EPA. (1998) inhalation assessment and the U.S. EPA (1999) extrapolation of the inhalation unit risk estimate to the oral route of exposure were externally peer reviewed. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A summary record of the comments and EPA responses is included as an appendix to the benzene support document file.

The EPA 1979 and 1985 documents provide the basis for the classification of benzene as a Group A carcinogen.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date:
inhalation carcinogenicity: 9/30/1998
oral carcinogenicity: 1/3/2000

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Benzene
CASRN — 71-43-2

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VII. Revision History

Benzene
CASRN — 71-43-2

Date	Section	Description
10/16/1998	II., VI.	Revised inhalation carcinogenicity section and references
01/19/2000	II., VI.	Revised oral carcinogenicity section and references
04/17/2003	IA., IB., VI.	New RfD and RfC sections; references.

VIII. Synonyms

Benzene
CASRN — 71-43-2
Last Revised — 01/19/2000

- 71-43-2
- Benzene
- benzol
- coal naphtha
- cyclohexatriene
- phene
- phenyl hydride
- polystream
- pyrobenzol