United States Environmental Protection Agency

EPA/690/R-09/003F
Final
9-29-2009

Provisional Peer-Reviewed Toxicity Values for

Benzene
(CASRN 71-43-2)

Derivation of a Subchronic Oral Provisional-RfD and a Subchronic Inhalation Provisional-RfC

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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR BENZENE (CASRN 71-43-2) DERIVATION OF A SUBCHRONIC ORAL PROVISIONAL-RfD AND A SUBCHRONIC INHALATION PROVISIONAL-RfC

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. U.S. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3. Other (peer-reviewed) toxicity values, including:
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

A streamlined approach was used to derive the provisional subchronic RfD and RfC values for benzene. Benzene has a chronic RfD, a chronic RfC, and a cancer assessment on IRIS; only derivation of the subchronic provisional toxicity values is presented. Benzene was recently reassessed by the IRIS program and a Toxicological Review (U.S. EPA, 2002) is available. In addition, the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for benzene has been updated recently (ATSDR, 2007). Both the IRIS Toxicological Review and the ATSDR Toxicological Profile contain comprehensive overviews of the toxicology and toxicokinetics available for benzene. Given the availability of recent IRIS and ATSDR reviews, these reports have been used in lieu of literature searches to identify the critical studies and endpoints for use in deriving the subchronic values.

The derivation of provisional subchronic toxicity values for benzene is discussed below. Review of the data supporting the chronic toxicity values for benzene on IRIS (U.S. EPA, 2003) indicated that subchronic data were used to derive the chronic values and, thus, are appropriate to serve as the basis for the corresponding subchronic toxicity values. A brief rationale is provided for the selection of the critical study and endpoint; a summary of the critical study is presented, and the subchronic toxicity value derivations are described. Further information on the toxicology and toxicokinetics of benzene is provided in Appendix A, Pertinent Sections from IRIS Summary for Benzene: Chronic Health Hazard Assessments for Noncarcinogenic Effects, the IRIS Toxicological Review for Benzene (U.S. EPA, 2002), or the ATSDR (2007) Toxicological Profile for Benzene.

REVIEW OF PERTINENT DATA AND DERIVATION OF PROVISIONAL SUBCHRONIC TOXICITY VALUES FOR BENZENE

The chronic RfC (0.03 mg/m^3) and the chronic RfD (0.004 mg/kg-day) for benzene on IRIS (U.S. EPA, 2002) were both based on hematological effects in humans exposed via inhalation in an occupational setting (Rothman et al., 1996). The mean duration of exposure in this study was 6.3 years (range 0.7–16 years), and a subchronic-to-chronic UF of 3 was applied in the derivation of both the RfC and RfD. The ATSDR intermediate-duration inhalation Minimal Risk Level (MRL) (0.006 ppm or 0.02 mg/m^3) was derived in August 2007 and is based on immunotoxicity in a 28-day study in mice (i.e., Rosenthal and Snyder, 1987). ATSDR (2007) reviewed two human occupational studies (inhalation exposure) of subchronic duration that were published after the IRIS (U.S. EPA, 2002) Toxicological Review: Lan et al. (2004) and Qu et al. (2002, 2003). Mean exposure durations in these studies were 6.1 and 4.5–9.7 years, respectively. Both studies identified statistically significant ($p < 0.05$) hematological effects at concentrations lower than the benchmark concentration lower bound $BMCL_{1SD}$ (8.2 mg/m^3) derived from the study by Rothman et al. (1996), which was used as the point of departure (POD) for deriving the chronic RfC on IRIS (U.S. EPA, 2002). The LOAEL identified by Lan et al. (2004) was 1.82 mg/m^3 and the LOAEL identified by Qu et al. (2002, 2003) was 7.22 mg/m^3. ATSDR (2007) applied BMD modeling to the data reported by Lan et al. (2004) to derive the chronic MRL for benzene (0.003 ppm or 0.01 mg/m^3). There is no intermediate-duration oral MRL for benzene, however, ATSDR (2007) derived a chronic oral MRL for benzene (0.0005 mg/kg-day) based on route-to-route extrapolation from the POD used to derive the chronic-duration inhalation MRL.

Given that the chronic RfC and RfD were derived recently and are based on a subchronic study, the subchronic p-RfC and p-RfD are based on the same critical study (i.e., Rothman et al., 1996), endpoint (hematological effects) and POD (BMCL of 8.2 mg/m^3; BMDL of 1.2 mg/kg-day) as the chronic values, without the UF_S factor (subchronic to chronic extrapolation).

A summary of the critical study is excerpted from the U.S. EPA (2008) IRIS record for benzene and reproduced below:

> *Rothman et al. (1996) conducted a cross-sectional study of 44 workers exposed to benzene and 44 age- and gender-matched unexposed controls. Of the 44 subjects in the exposed and control groups, 21 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 work shift 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.*

There were six hematological measurements that were evaluated: total white blood cell (WBC) count, absolute lymphocyte count (ALC), hematocrit, red blood cell (RBC) count, platelet count and mean corpuscular volume (MCV) (Rothman et al., 1996). 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 × 10^3/μL blood in controls to 1.6 × 10^3/μL ($p < 0.01$) in the <31 ppm group and to 1.3 × 10^3/μL ($p < 0.001$) in the group exposed to >31 ppm benzene. The ALC was also significantly reduced (1.6 × 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.*

As noted above, subchronic toxicity values for benzene are based on the same critical study, endpoint, and POD as the corresponding IRIS chronic toxicity values.

Derivation of a Subchronic p-RfD for Benzene

For the chronic RfD, U.S. EPA (2002) utilized route-to-route extrapolation from the POD used to derive the chronic RfC. A $BMCL_{1SD}$ (the lower confidence limit on the benchmark concentration associated with a benchmark response of 1 standard deviation [SD] from the control mean response) of 8.2 mg/m^3 was estimated from modeling the data on lymphocyte count in humans exposed via inhalation (Rothman et al., 1996). The $BMCL_{1SD}$ was converted to an equivalent oral dose of 1.2 mg/kg-day, which was then used as the POD for derivation of the chronic RfD. The text below, excerpted from the IRIS record for benzene, briefly describes the extrapolation procedure. Further details on the BMD modeling and the route-to-route extrapolation are available in the IRIS Summary (see Appendix A) and in the Toxicological Review (U.S. EPA, 2002).

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.

To derive the chronic RfD (0.004 mg/kg-day), the extrapolated POD (1.2 mg/kg-day) was divided by a composite UF of 300, which includes a 10-fold UF for intraspecies variation, a 3-fold UF for use of an adverse effect level, a 3-fold UF for extrapolation from subchronic-to-chronic duration, and a 3-fold UF for database deficiencies—especially the lack of multigeneration reproductive toxicity and developmental toxicity studies. Appendix A contains additional details on the UF selections.

For the derivation of a subchronic p-RfD, the BMDL-equivalent value of 1.2 mg/kg-day was divided by a composite UF of 100, including a 10-fold UF for intraspecies variation, a 3-fold UF for use of an adverse effect level, and a 3-fold UF for database deficiencies. This composite UF differs from the chronic composite UF by a factor of 3 because there is no extrapolation to chronic exposure. Derivation of the **subchronic p-RfD** is show below.

Subchronic p-RfD = POD ÷ UF
= 1.2 ÷ 100
= **0.01 or 1 × 10^{-2} mg/kg-day**

Confidence in the subchronic p-RfD is medium, which is identical with the IRIS chronic RfD. As discussed further in the IRIS Summary and Toxicological Review for benzene, the principal study of Rothman et al. (1996) is well conducted, and a dose-response relationship was established between ALC and benzene air concentration and benzene urine metabolites. In addition, the RfD obtained from route-to-route extrapolation of the BMD modeling results from the Rothman et al. (1996) study is in good agreement with effect levels identified in male rats based on ALC data from the NTP (1986) chronic rodent gavage study. Further, while route-to-route extrapolation was used to estimate a POD, this extrapolation introduces less uncertainty than extrapolating from test animals to humans (U.S. EPA, 1999).

Derivation of a Subchronic p-RfC for Benzene

For the chronic RfC, U.S. EPA (2002) estimated a $BMCL_{1SD}$ of 8.2 mg/m^3 from BMD modeling of the data on lymphocyte count in humans exposed via inhalation (Rothman et al., 1996). The $BMCL_{1SD}$ was used as the POD for derivation of the chronic RfC. Further detail on the BMD modeling is available in the IRIS Summary (see Appendix A) and in the Toxicological Review (U.S. EPA, 2002). A composite UF of 300 was applied to the $BMCL_{1SD}$ to derive the chronic RfC. The composite UF includes a 10-fold UF for intraspecies variation, a 3-fold UF for use of an adverse effect level, a 3-fold UF for extrapolation from subchronic-to-chronic duration, and a 3-fold UF for database deficiencies—especially the lack of multigeneration reproductive toxicity and developmental toxicity studies. Appendix A contains additional details on the UF selections.

For the derivation of a subchronic p-RfC, the $BMCL_{1SD}$ of 8.2 mg/m^3 was divided by a composite UF of 100 that includes a 10-fold UF for intraspecies variation, a 3-fold UF for use of an adverse effect level, and a 3-fold UF for database deficiencies. This composite UF differs from the chronic composite UF by a factor of 3 because there is no extrapolation to chronic exposure. Derivation of the **subchronic p-RfC** is shown below.

Subchronic p-RfC = POD ÷ UF
= 8.2 ÷ 100
= **0.08 or 8 × 10^{-2} mg/m^3**

Confidence in the subchronic p-RfC is medium, which identical with the IRIS chronic RfC. As discussed further in the IRIS Summary and Toxicological Review for benzene, the principal study of Rothman et al. (1996) is well conducted, and a dose-response relationship was established between ALC and benzene air concentration and benzene urine metabolites. 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 obtained from the BMD modeling results from the Rothman et al. (1996) study is in good agreement with the effect levels identified from the Ward et al. (1985) subchronic rodent inhalation study.

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APPENDIX A. PERTINENT SECTIONS FROM IRIS SUMMARY FOR BENZENE: CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

Benzene; CASRN 71-43-2; 04/17/2003

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Benzene

File First On-Line 03/01/1988

Category (section)		
Oral RfD Assessment (I.A.)	online	04/17/2003
Inhalation RfC Assessment (I.B.)	online	04/17/2003
Carcinogenicity Assessment (II.)	online	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				
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 $10^3/\mu L$ blood in controls to 1.6 x $10^3/\mu L$ (p <0.01) in the <31 ppm group and to 1.3 x $10^3/\mu L$ (p<0.001) in the group exposed to >31 ppm benzene. The ALC was also significantly reduced (1.6 x $10^3/\mu L$; 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).

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;

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
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.)

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 x 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 x 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 x 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 x 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).

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_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 x 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 $mg/m^3 \div 1000 = 9 \times 10^{-3}$ 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 9×10^{-3} mg/m^3 is in good agreement with the RfC of 3×10^{-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).

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_*VI. Bibliography*

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

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