Bromobenzene; CASRN 108-86-1

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 BROMOBENZENE

File First On-Line 09/30/2009

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)		
Subchronic Oral RfD (I.A.1)	yes	09/30/2009
Chronic Oral RfD (I.A.2)	yes	09/30/2009
Inhalation RfC (I.B.)		
Subchronic Inhalation RfC (I.B.1)	yes	09/30/2009
Chronic Inhalation RfC (I.B.2)	yes	09/30/2009
Carcinogenicity (II.)	yes	09/30/2009

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) SUBCHRONIC AND CHRONIC ORAL EXPOSURE

Bromobenzene
CASRN — 108-86-1
Section I.A. Last Revised — 09/30/2009

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

This is the first IRIS assessment for bromobenzene. No oral subchronic or chronic RfD for bromobenzene was previously available on IRIS.

I.A.1. SUBCHRONIC ORAL RfD

I.A.1.1. SUBCHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Subchronic RfD
Hepatocellular cytomegaly in male B6C3F$_1$ mice **90-day oral gavage administration** **NTP (1985b)**	$BMDL_{10}$: 33.8 mg/kg-day Duration adjusted $BMDL_{10}$: 24.1 mg/kg-day	1,000	2×10^{-2} mg/kg-day

*Conversion Factors and Assumptions -- The $BMDL_{10}$ of 33.8 mg/kg-day was adjusted to reflect continuous daily exposure (33.8 mg/kg-day × 5/7 days = 24.1 mg/kg-day).

I.A.1.2. PRINCIPAL AND SUPPORTING STUDIES

Studies on health effects in humans exposed to bromobenzene are not available. The National Toxicology Program (NTP) conducted subchronic gavage studies of bromobenzene in rats (NTP, 1985a) and mice (NTP, 1985b). These unpublished reports, including the review comments and conclusions of the Pathology Working Group (NTP, 1986a), were obtained from NTP. Both the rat and mouse studies were considered for use as the principal study for deriving the subchronic RfD because they both include adequate dose-response information, and no other comprehensive repeated dose oral studies are available for bromobenzene.

Groups of 10 male and 10 female F344/N rats (NTP, 1985a) and $B6C3F_1$ mice (NTP, 1985b) were given 0, 50, 100, 200, 400, or 600 mg/kg-day of bromobenzene (>99% purity) by gavage in corn oil 5 days/week for 90 days. Blood samples were collected on days 2, 4, 24, and 95 for hematology and clinical chemistry. Blood samples for hematologic and clinical pathologic examinations were collected from all surviving rats and mice at terminal sacrifice. Terminal body and organ (liver, brain, testis, kidney, lung, heart, and thymus) weights were recorded; organ-to-body weight and organ-to-brain weight ratios were calculated for each sex. Complete gross necropsy was performed on all rats and mice. Complete histopathologic examinations of all major tissues and organs were performed on all control rats and mice and all rats and mice from the 400 and 600 mg/kg-day dose groups. Histopathologic examination of the liver was performed for all control and bromobenzene-treated rats and mice. Kidney histopathology was assessed in all groups of rats and all but the 50 and 100 mg/kg-day groups of mice.

Comprehensive examinations of all major tissues and organs in the subchronic studies of rats and mice revealed no significantly increased incidences of exposure-related effects other than in the liver and kidney. Liver observations included increased liver weights and serum enzymes, and increased incidence of inflammation, cytomegaly, necrosis, and mineralization in male and female rats and mice (NTP, 1985a, b). Significantly increased mean liver weights were observed at bromobenzene doses as low as 50 mg/kg-day in female F344/N rats and $B6C3F_1$ mice and 100 mg/kg-day in the male rats and mice. Dose levels of 400 and 600 mg/kg-day resulted in ≥twofold increases (statistically and/or biologically significant) in serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and sorbitol dehydrogenase (SDH) in male and female rats, and increased SDH in male and female mice. Statistically significant increased incidences of liver inflammation were observed at doses ≥200 mg/kg-day in male rats (also increased in females but incidence did not reach statistical significance compared to controls). Significantly increased incidences of hepatocellular necrosis were observed at doses of 400 and 600 mg/kg-day in male and female rats and male mice (600 mg/kg-day in female mice) (NTP, 1985a, b). Hepatic mineralization was slightly increased in male and female rats and female mice in the 600 mg/kg-day dose group, and significantly increased in male mice at doses ≥400 mg/kg-day. Significantly

increased incidences of hepatocellular cytomegaly were observed at doses ≥200 mg/kg-day in male rats (≥400 mg/kg-day in female rats) and male and female mice. Significantly increased incidences of kidney lesions were also observed in male and female rats and mice (NTP, 1985a, b). These kidney lesions were associated with the proximal convoluted tubule and consisted of degeneration, casts, necrosis (rats only), and mineralization. The incidence of kidney lesions was not considered for the development of the subchronic RfD because the lowest dose associated with a statistically significant increase in the incidence of renal lesions (600 mg/kg-day in rats and mice) was higher than the lowest dose (200 mg/kg-day rats and mice) resulting in a treatment-related liver effect (e.g., hepatocellular cytomegaly). Thus, the liver effects are a more sensitive indicator of oral bromobenzene toxicity.

The mouse study (NTP, 1985b) was selected as the principal study for deriving the subchronic RfD, and hepatocellular cytomegaly was selected as the critical effect. The significantly increased absolute and relative liver weights, observed in conjunction with the increased levels of systemically circulating liver enzymes and increased incidence of cytomegaly, necrosis, inflammation, and mineralization in the livers of both rats and mice are all considered manifestations of bromobenzene exposure (NTP, 1985a, b). There is some evidence to suggest that bromobenzene-induced cytomegaly, inflammation, necrosis, and mineralization are part of a pathological continuum. Specifically, all four lesions were primarily observed in the central region of the hepatic lobules of treated rats. Furthermore, mechanistic data suggest several potential bromobenzene-induced cellular alterations that could individually, or in concert, commit hepatocytes to mixed cellular phenotypes consistent with the histopathological observations in rats and mice of the NTP studies (1985a, b). In the NTP oral route studies, inflammation and mineralization were considered to be causally associated with or a direct result of, respectively, hepatocellular necrosis (NTP, 1986a, 1985a, b). However, the observed incidence of hepatic inflammation in the control and lower dose (<200 mg/kg-day) groups of bromobenzene-treated male and female rats and mice, in the absence of evidence of hepatocellular necrosis, suggests that this lesion may not be associated directly with cell injury, at least not at lower doses, and was therefore not further considered. The hepatic mineralization was observed only at the highest bromobenzene dose (600 mg/kg-day) in male and female rats and male mice (at 400 mg/kg-day in female mice), the same dose at which mortality occurred. Liver lesions, such as mineralization, observed at a high dose frank effect level (FEL) are of limited usefulness for quantitative evaluation of bromobenzene-induced toxicity. Importantly, liver cytomegaly observed in the NTP studies (NTP, 1985a, b) was identified and described by pathologists as an "enlargement of both the cell and the nucleus" (NTP, 1986a). It should be noted that necrotic cell death is commonly referred to as "oncosis" or "oncotic" necrosis; oncotic meaning "pertaining to, caused by or marked by swelling" (for review, Van Cruchten and Van Den Broeck, 2002). Thus, the histopathological identification of liver cytomegaly at lower doses of bromobenzene (e.g., 200 mg/kg-day in male mice) by NTP (1985a, b) may be an early indication of hepatocyte injury, to potentially

include some state of oncotic cell death. Cytomegaly may also represent an adverse effect regardless of a potential association with necrosis. Cytomegaly is selected as the critical effect to serve as the basis for the derivation of the subchronic RfD as it represents the most sensitive exposure-related histopathological endpoint in the liver.

All available models in the EPA BMDS (version 1.4.1) were fit to the incidence data for animals with liver cytomegaly. Modeling results are presented in Appendix B of the *Toxicological Review of Bromobenzene* (U.S. EPA, 2009).

The male mouse liver lesion data produced the lowest $BMDL_{10}$ (33.8 mg/kg-day). The benchmark response (BMR) of 10% extra risk (U.S. EPA, 2000) was selected because in the absence of biological information that would warrant a different choice, a 10% increase in incidence relative to controls is considered representative of a minimal biological significant change. As such, liver toxicity in male mice, as defined by an increase in the incidence of liver cytomegaly, was selected as the critical effect for deriving the subchronic RfD. The $BMDL_{10}$ of 33.8 mg/kg-day (duration adjusted $BMDL_{10}$ = 24.1 mg/kg-day) was selected as the point of departure to derive the subchronic RfD for bromobenzene.

I.A.1.3. UNCERTAINTY FACTORS

UF = 1,000

The composite UF of 1,000 consists of three areas of uncertainty: (1) interspecies extrapolation, (2) interindividual human variability, and (3) database deficiencies.

A 10-fold UF for laboratory animal-to-human interspecies differences (UF_A) was applied to account for the variability in extrapolating from mice to humans. No information is available on toxicokinetic or toxicodynamic differences or similarities for bromobenzene in animals and humans. In the absence of data to quantify specific toxicokinetic and toxicodynamic differences, a default factor of 10 was applied.

A 10-fold UF for intraspecies differences (UF_H) was applied to account for variability in susceptibility in human populations. The default value of 10 was selected in the absence of information indicating the degree to which humans may vary in susceptibility to bromobenzene hepatotoxicity.

An UF of 1 for LOAEL-to-NOAEL extrapolation was applied because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% change in the incidence of liver cytomegaly was selected under an assumption that it represents a minimal biologically significant change.

A 10-fold UF was used to account for database deficiencies (UF_D). Subchronic studies in rats and mice are available. Developmental toxicity and multi-generation reproductive toxicity studies are lacking for bromobenzene. The subchronic gavage studies of bromobenzene in rats and mice did not reveal evidence of significant treatment-related effects on reproductive organs or tissues at dose levels that were hepatotoxic (NTP, 1985a, b). Additionally, bromobenzene and chlorobenzene exhibit similarities in structure, toxicokinetic properties, and critical target of toxicity (liver) in rats and mice (see Section 4.5.4 for a detailed discussion). Therefore, the toxicity database for chlorobenzene was assessed for its potential to address database deficiencies for bromobenzene. In a two-generation reproductive toxicity study in rats, chlorobenzene did not induce developmental effects in the fetuses of pregnant rats exposed to oral dose levels of 100 or 300 mg/kg-day on gestation days 6-15 (IBT, 1977). However, reproductive effects, in particular multi-generational effects, may be important to informing the bromobenzene toxicity database considering the high DNA reactivity of this chemical. Bromobenzene was second only to 1,2 dibromoethane in its relative in vivo reactivity with rat liver DNA, exhibiting higher reactivity than 1,2-dichloroethane, chlorobenzene, epichlorohydrin, and benzene (Prodi et al., 1986). Therefore, the lack of a multi-generational study is of particular concern because genetic damage to germ cells of an F1 generation may not be detected until the F2 generation. In the absence of any information concerning reproductive and developmental endpoints following bromobenzene exposure, an UF of 10 was applied.

I.A.1.4. ADDITIONAL STUDIES/COMMENTS

The toxic effects of bromobenzene following acute exposure have been extensively studied. Liver, kidney, and lung have been identified as the target organs for this chemical by a variety of routes. Histopathologic examinations have revealed necrotic changes in all of these organs following short-term bromobenzene exposure (Szymańska and Piotrowski, 2000; Szymańska, 1998; Casini et al., 1986; Forkert, 1985; Kluwe et al., 1984; Rush et al., 1984; Roth, 1981; Reid et al., 1973; Patrick and Kennedy, 1964).

The liver is the most sensitive target following acute oral exposure. In rats given single oral doses of bromobenzene by gavage, a dose of 39 mg/kg-day resulted in reduced hepatic glutathione; a higher dose (157 mg/kg-day) resulted in moderate periportal and midzonal hydropic changes, while increased serum liver enzyme levels and hepatic centrilobular necrosis were observed following dosing at 314 mg/kg-day (Kluwe et al., 1984). In the same study, renal glutathione was reduced at a dose of 157 mg/kg-day, but no other renal effects were noted at doses up to 628 mg/kg-day. Other acute oral studies reported hepatic necrosis in rats (Heijne et al., 2004) or mice (Patrick and Kennedy, 1964) administered bromobenzene at doses in the range of 500-700 mg/kg.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.1.5. CONFIDENCE IN THE SUBCHRONIC ORAL RfD

Study — Medium
Data Base — Low to Medium
RfD — Medium

The overall confidence in the subchronic RfD is medium. The principal study is an adequate gavage study of subchronic duration and is supported by a similarly-designed study in a second animal species; however, due to a low number of animals per treatment group (10/group), the confidence in the principal study is medium. Confidence in the database is low-to-medium. Studies assessing the developmental toxicity and multi-generation reproductive toxicity of bromobenzene are lacking.

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

I.A.2. CHRONIC ORAL RfD

I.A.2.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Hepatocellular cytomegaly in male B6C3F$_1$ mice **90-day oral gavage administration** **NTP (1985b)**	$BMDL_{10}$: 33.8 mg/kg-day Duration adjusted $BMDL_{10}$: 24.1 mg/kg-day	3,000	8×10^{-3} mg/kg-day

*Conversion Factors and Assumptions -- The $BMDL_{10}$ 33.8 mg/kg-day was adjusted reflect continuous daily exposure (33.8 mg/kg-day × 5/7 days = 24.1 mg/kg-day).

I.A.2.2. PRINCIPAL AND SUPPORTING STUDIES

As discussed in Section 4.1 of the *Toxicological Review of Bromobenzene* (U.S. EPA, 2009), there are no human studies available for development of a chronic RfD. The toxicity studies

for repeated oral exposure in laboratory animals that are available for selection of an RfD consist of two 90-day gavage studies—one in rats (NTP, 1985a) and one in mice (NTP, 1985b). No chronic-duration, reproductive toxicity, or developmental toxicity studies are available. For these reasons, the principal study (NTP, 1985b) and critical effect (cytomegaly) for development of the chronic RfD for bromobenzene is the same as that described for the development of the subchronic RfD (see Section 5.1.1.1).

I.A.2.3. UNCERTAINTY FACTORS

UF = 3,000

The UF consists of four areas of uncertainty: (1) interspecies extrapolation, (2) interindividual human variability, (3) subchronic to chronic duration extrapolation, and (4) database deficiencies.

A 10-fold UF for laboratory animal-to-human interspecies differences (UF_A) was applied to account for the variability in extrapolating from mice to humans. No information is available on toxicokinetic or toxicodynamic differences or similarities for bromobenzene in animals and humans. In the absence of data to quantify specific toxicokinetic and toxicodynamic differences, a default factor of 10 was applied.

A 10-fold UF for intraspecies differences (UF_H) was applied to account for variability in susceptibility in human populations. The default value of 10 was selected in the absence of information indicating the degree to which humans may vary in susceptibility to bromobenzene hepatotoxicity.

A factor of 3 UF was applied to account for extrapolating from a subchronic study to chronic exposure scenarios (UF_S). Subchronic oral studies in both male and female rats and mice identify the liver as a critical target of bromobenzene toxicity. As discussed in Section 4.5, the liver develops a tolerance to bromobenzene insult during repeated exposure. For example, a single 315 mg/kg oral dose of bromobenzene administered to male rats resulted in marked glutathione depletion, increased serum ALT and SDH concentrations, and observed histopathologic liver lesions (Kluwe et al., 1984). Following 10 days of dosing at 315 mg/kg-day, glutathione depletion was less pronounced, serum ALT and SDH concentrations were no longer increased, and histopathologic liver lesions were no longer detected. Furthermore, as discussed in detail in Section 4.5.4, bromobenzene and chlorobenzene exhibit similarities in structure, toxicokinetic properties, and critical target of toxicity (liver) in rats and mice. In a subchronic (90-day) oral toxicity study in mice, a NOAEL of 125 and a LOAEL of 250 mg/kg-day were identified in both males and females for chlorobenzene-induced liver lesions (NTP, 1985e). In a similarly-designed NTP 2 year oral study of chlorobenzene, nonneoplastic

lesions attributable to chlorobenzene were not observed in male and female mice; NTP identified freestanding NOAELs of 60 and 120 mg/kg-day, respectively (NTP, 1985e). These results suggest that the dose-response relationships for liver effects from subchronic and chronic exposure may be similar. It is reasonable to expect such similarities in dose-response relationships for subchronic and chronic exposure to bromobenzene due to the similarity between the two chemicals with respect to chemical reactivity and structure, including similar Pauling electronegativities of chlorine (3.16) and bromine (2.96) (Loudon, 1988).

An UF of 1 for LOAEL-to-NOAEL extrapolation was applied because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% change in the incidence of liver cytomegaly was selected under an assumption that it represents a minimal biologically significant change.

A 10-fold UF was applied to account for database deficiencies (UF_D). Subchronic studies in rats and mice are available. As discussed previously (Section 5.1.1.3), the oral database for bromobenzene lacks developmental toxicity and multi-generation reproductive toxicity studies. The subchronic gavage studies of bromobenzene in rats and mice did not reveal evidence of significant treatment-related effects on reproductive organs or tissues at dose levels that were hepatotoxic (NTP, 1985a, b). Additionally, bromobenzene and chlorobenzene exhibit similarities in structure, toxicokinetic properties, and critical target of toxicity (liver) in rats and mice (see Section 4.5.4 for a detailed discussion). Therefore, the toxicity database for chlorobenzene was assessed for its potential to address database deficiencies for bromobenzene. In a two-generation reproductive toxicity study in rats, chlorobenzene did not induce developmental effects in the fetuses of pregnant rats exposed to oral dose levels of 100 or 300 mg/kg-day on gestation days 6-15 (IBT, 1977). However, reproductive effects, in particular multi-generational effects, may be important to informing the bromobenzene toxicity database considering the high DNA reactivity of this chemical. Bromobenzene was second only to 1,2 dibromoethane in its relative in vivo reactivity with rat liver DNA, exhibiting higher reactivity than 1,2-dichloroethane, chlorobenzene, epichlorohydrin, and benzene (Prodi et al., 1986). Therefore, the lack of a multi-generational study is of particular concern because genetic damage to germ cells of an F1 generation may not be detected until the F2 generation. In the absence of any information concerning reproductive and developmental endpoints following bromobenzene exposure, an UF of 10 was applied.

I.A.2.4. ADDITIONAL STUDIES/COMMENTS

Additional studies/comments for the subchronic oral RfD (see Section I.A.1.4) apply to the derivation of the chronic oral RfD.

I.A.2.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study — Medium
Data Base — Low-to-Medium
RfD — Low-to-Medium

The overall confidence in the chronic RfD is low-to-medium. Since there are no known chronic duration oral studies available, the RfD is based upon a subchronic duration study (NTP, 1985b). The principal study is an adequate gavage study and is supported by a similarly-designed study in a second animal species; however, due to a low number of animals per treatment group (10/group), the confidence in the principal study is medium. Confidence in the database is low-to-medium. Studies assessing the developmental toxicity and multi-generation reproductive toxicity of bromobenzene are lacking.

I.A.3. EPA DOCUMENTATION AND REVIEW OF THE SUBCHRONIC AND CHRONIC ORAL RfD

Source Document — U.S. EPA. (2009).

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to the EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Bromobenzene* (U.S. EPA, 2009). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

I.A.4. EPA CONTACTS

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 (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR SUBCHRONIC AND CHRONIC INHALATION EXPOSURE

Bromobenzene
CASRN — 108-86-1
Section I.B. Last Revised — 09/30/2009

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

This is the first IRIS assessment for bromobenzene. No inhalation subchronic or chronic RfC for bromobenzene was previously available on IRIS.

I.B.1. SUBCHRONIC INHALATION RfC

I.B.1.1. SUBCHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Subchronic RfC
Hepatocellular cytomegaly in female B6C3F$_1$ mice **13-week inhalation study** **NTP (1985d)**	$BMCL_{10}$: 55 ppm $BMCL_{10HEC}$: 63 mg/m^3	300	2×10^{-1} mg/m^3

*Conversion Factors and Assumptions — Following U.S. EPA (1994) methodology, the human equivalent concentration (HEC) for an extra respiratory effect produced by a category 3 gas, is calculated by multiplying the duration-adjusted BMCL by the ratio of the blood:gas partition coefficients in animals and humans $[(H_{b/g})_A / H_{b/g})_H]$. Because bromobenzene blood:gas partition coefficients are not available for humans or mice, a default value of 1 was used for this ratio. The averaged $BMCL_{10}$ of 55 ppm for hepatocellular cytomegaly in female mice was converted to 353.2 mg/m^3 (55 ppm × MW[157] / 24.45 = 353.2 mg/m^3), which was

then converted to reflect continuous exposure (353.2 mg/m^3 × 6/24 hours × 5/7 days = 63 mg/m^3) and multiplied by a default blood:gas partition coefficient ratio of 1 to obtain the $BMCL_{10HEC}$ of 63 mg/m^3.

I.B.1.2. PRINCIPAL AND SUPPORTING STUDIES

No data are available on health effects in humans following inhalation exposure to bromobenzene. Pertinent information on health effects in animals is restricted to results from studies in male and female F344/N rats (NTP, 1985c) and $B6C3F_1$ mice (NTP, 1985d) repeatedly exposed to bromobenzene vapors for 13 weeks. These studies have not been officially released by NTP, but unpublished reports, including the review comments and conclusions of NTP's Pathology Working Group (NTP, 1986b), were obtained from NTP. Both the rat and mouse studies were considered for use as the principal study for deriving the RfC because they both include exposure-response information and no other comprehensive subchronic inhalation studies are available for bromobenzene.

Groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice were exposed to bromobenzene vapors through whole-body exposure at 0, 10, 30, 100, or 300 ppm (0, 64.2, 192.6, 642, or 1,926 mg/m^3) 6 hours/day, 5 days/week for 13 weeks (the mouse study did not include 300 ppm males). Animals were observed twice daily for morbidity and mortality. Clinical observations and body weight measurements were performed weekly. Blood samples for hematologic examination (erythrocyte and leukocyte counts; hemoglobin concentrations; red blood cell indices of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin content (MCHC); leukocyte differential counts) were collected from all surviving animals at terminal sacrifice. Terminal body and organ (liver, brain, testis, kidney, lung, heart, and thymus) weights were recorded; organ-to-body weight and organ-to-brain weight ratios were calculated for each sex and species. Complete gross necropsy was performed on all animals. Complete histopathologic examinations of all major tissues and organs were performed on all control rats and mice and all rats and mice from the highest exposure levels (100 ppm for male mice, 300 ppm for male and female rats and female mice). In addition, histopathologic examinations were performed on liver tissue from all control and bromobenzene-exposed male and female mice of each group. Kidney tissue was examined histopathologically in control and 300 ppm female rats and all groups of male rats and male and female mice.

The liver appeared to be the most sensitive toxicity target (NTP, 1986b, 1985c,d). Liver weights (absolute and relative) were significantly increased at exposure concentrations ≥100 ppm in both sexes of rats. In mice, absolute liver weight was not affected at any inhalation concentration tested in males however, increased liver weight was observed in females at concentrations ≥ 30 ppm. The liver-to-body weight ratio was significantly increased in 100

ppm male mice (the study did not include a 300 ppm male group) and in females at concentrations ≥ 10 ppm. Compared to controls, no significant increase in liver lesions were observed in male or female rats at the highest inhalation doses examined (300 ppm). A significantly increased incidence of cytomegaly was observed in 300 ppm female mice (10/10 versus 0/10 controls). Necrosis was noted in 5/10 of the 300 ppm female mice, but the incidence of this lesion was not significantly greater than the incidence in controls (2/10).

In rats, renal histopathology was associated with bromobenzene only at the highest exposure level tested (300 ppm) (NTP, 1985c). Although this lesion was observed in all male rats of the highest exposure group, it was also noted (albeit in slightly lesser severity) in all control males. The increased severity of the renal lesion (cortical tubular regeneration without observable degeneration or necrosis) at the highest exposure level (300 ppm) may represent a treatment-related renal effect in the male rats. However, the Pathology Working Group considered this effect to be mild in all rats in the high-exposure group (NTP, 1986b). Exposure of female rats at levels up to and including 300 ppm did not result in exposure-related adverse renal effects. Evidence of exposure-related renal effects was not detected in the male or female mice at exposure concentrations up to and including the highest level tested (300 ppm for females; 100 ppm for males). Comprehensive histopathologic examinations of all major tissues and organs in the subchronic inhalation studies of rats and mice revealed no clear evidence of exposure-related lesions at sites other than the kidney (rats) and liver (mice).

All available models in U.S. EPA BMDS were fit to the liver lesion (cytomegaly) data for female B6C3F_1 mice from the 90-day inhalation studies (NTP, 1985d). Modeling results are presented in Appendix C of the *Toxicological Review of Bromobenzene* (U.S. EPA, 2009). The $BMCL_{10}$ values from the best-fitting models of cytomegaly in female mice (from the log-logistic and gamma models) were averaged (55 ppm) to arrive at the point of departure for deriving the RfC. A 10% extra risk level was selected as the BMR for cytomegaly. The BMR of 10% extra risk was selected in the absence of biological information that would warrant a different choice is considered representative of a minimal biological significant change.

I.B.1.3. UNCERTAINTY FACTORS

UF = 300

The POD was divided by a total UF of 300. The UF consists of three areas of uncertainty: (1) interspecies extrapolation, (2) interindividual human variability, and (3) database deficiencies.

A factor of 3 was applied to account for uncertainties in extrapolating from mice to humans (UF_A). This value is adopted by convention where an adjustment from an animal-specific $BMCL_{ADJ}$ to a $BMCL_{HEC}$ has been incorporated. Application of an UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component associated with bromobenzene is mostly addressed by the determination of an HEC as described in the RfC methodology (U.S. EPA, 1994b). The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method, and a UF of 3 is retained to account for uncertainty regarding the toxicodynamic differences between mice and humans.

A default 10-fold UF was applied to account for interindividual toxicokinetic and toxicodynamic variability in humans (UF_H) in the absence of information concerning the extent of variation in sensitivity to bromobenzene within the human population.

An UF for extrapolation from a LOAEL to NOAEL (UF_L) was not needed because the current approach is to address this extrapolation as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% increase in the incidence of cytomegaly was selected under an assumption that it represents a minimal biologically significant change.

A 10-fold UF was applied to account for database deficiencies (UF_D). Subchronic studies in rats and mice are available. Developmental toxicity and multi-generation reproductive toxicity studies are lacking. It should be noted that bromobenzene and chlorobenzene exhibit similarities in structure, toxicokinetic properties, and critical target of toxicity (liver) in rats and mice (see Section 4.5.4 for a detailed discussion). Therefore, the toxicity database for chlorobenzene was assessed for its potential to address database deficiencies for bromobenzene. For example, in a two-generation reproductive toxicity study in rats, chlorobenzene did not elicit any signs of reproductive toxicity in either generation at an exposure level of 450 ppm (Nair et al., 1987). In the same study, both F0 and F1 male rats exhibited chlorobenzene-induced hepatotoxicity from inhalation exposure at concentrations as low as 150 ppm. Chlorobenzene did not induce developmental effects in the fetuses of pregnant rats exposed to vapor concentrations as high as 590 ppm for 6 hours/day on gestation days 6-15 (John et al., 1984) (IBT, 1977). However, reproductive effects, in particular multi-generational effects, may be important to informing the bromobenzene toxicity database

considering the high DNA reactivity of this chemical. Bromobenzene was second only to 1,2 dibromoethane in its relative in vivo reactivity with rat liver DNA, exhibiting higher reactivity than 1,2-dichloroethane, chlorobenzene, epichlorohydrin, and benzene (Prodi et al., 1986). Therefore, the lack of a multi-generational study is of particular concern because genetic damage to germ cells of an F1 generation may not be detected until the F2 generation. In the absence of any information concerning reproductive and developmental endpoints following bromobenzene exposure, an UF of 10 was applied.

I.B.1.4. ADDITIONAL STUDIES/COMMENTS

The effects of bromobenzene following acute exposure have been extensively studied. Liver, kidney, and lung have been identified as the target organs for this chemical by a variety of routes. Histopathologic examinations have revealed necrotic changes in all of these organs following short-term bromobenzene exposure (Szymańska and Piotrowski, 2000; Szymańska, 1998; Becher et al., 1989; Casini et al., 1986; Forkert, 1985; Kluwe et al., 1984; Rush et al., 1984; Roth, 1981; Reid et al., 1973; Patrick and Kennedy, 1964). Serum liver enzyme changes were observed in rats exposed to a bromobenzene vapor concentration of 107 ppm for 4 hours (Brondeau et al., 1983). Extrahepatic effects observed in other acute inhalation studies included pulmonary effects, seen as moderate vacuolization of pulmonary Clara cells in mice exposed to 250 ppm for 4 hours (Becher et al., 1989), and pulmonary necrosis in mice exposed to 1,000 ppm for 4 hours (Becher et al., 1989). However, lung lesions were not seen in rats or mice repeatedly exposed to bromobenzene vapors at concentrations up to 300 ppm (NTP, 1985c,d).

I.B.1.5. CONFIDENCE IN THE SUBCHRONIC INHALATION RfC

Study — Medium
Data Base — Low-to-Medium
RfC — Medium

The overall confidence in the subchronic RfC is medium. The principal study is an inhalation study of subchronic duration that reported significantly increased incidence of hepatocellular cytomegaly in female mice. Due to a low number of animals per treatment group (10/group), the confidence in the principal study is medium. Confidence in the database is low-to-medium. Studies assessing the developmental toxicity and multi-generation reproductive toxicity of bromobenzene are lacking.

I.B.2. CHRONIC INHALATION RfC

I.B.2.1 CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC
Hepatocellular cytomegaly in female B6C3F$_1$ mice **13-week inhalation study** **NTP (1985d)**	$BMCL_{10}$: 55 ppm $BMCL_{10HEC}$: 63 mg/m^3	1,000	6×10^{-2} mg/m^3

*Conversion Factors and Assumptions — Following U.S. EPA (1994) methodology, the HEC for an extra respiratory effect produced by a category 3 gas, the liver as the critical extrarespiratory target), is calculated by multiplying the duration-adjusted BMCL or NOAEL by the ratio of the blood:gas partition coefficients in animals and humans [$(H_{b/g})_A$ / $H_{b/g})_H$]. Because bromobenzene blood:gas partition coefficients are not available for humans or mice, a default value of 1 was used for this ratio. The averaged $BMCL_{10}$ of 55 ppm for hepatocellular cytomegaly in female mice was converted to 353.2 mg/m^3 (55 ppm × MW[157] / 24.45 = 353.2 mg/m^3), which was then converted to reflect continuous exposure (353.2 mg/m^3 × 6/24 hours × 5/7 days = 63 mg/m^3) and multiplied by a default blood:gas partition coefficient ratio of 1 to obtain the $BMCL_{10HEC}$ of 63 mg/m^3.

I.B.2.2. PRINCIPAL AND SUPPORTING STUDIES

The database of information regarding the toxicity of bromobenzene following repeated inhalation exposure consists of subchronic studies of bromobenzene in rats (NTP, 1985c) and mice (NTP, 1985d). No chronic duration inhalation studies are available. The discussion of principal and supporting studies for the subchronic RfC (see Section I.B.1.2) applies to the derivation of the chronic RfC.

I.B.2.3. UNCERTAINTY FACTORS

UF = 1,000

The UF consists of four areas of uncertainty: (1) interspecies extrapolation, (2) interindividual human variability, (3) extrapolation from subchronic-to- chronic duration exposure, and (4) database deficiencies.

A factor of 3 was applied to account for uncertainties in extrapolating from mice to humans (UF_A). This value is adopted by convention where an adjustment from an animal-specific $BMCL_{ADJ}$ to a $BMCL_{HEC}$ has been incorporated. Application of an UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component associated with bromobenzene is mostly addressed by the determination of an HEC as described in the RfC methodology (U.S. EPA, 1994b). The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method, and an UF of 3 is retained to account for uncertainty regarding the toxicodynamic differences between mice and humans.

A default 10-fold UF was applied to account for interindividual toxicokinetic and toxicodynamic variability in humans (UF_H) in the absence of information concerning the extent of variation in sensitivity to bromobenzene within the human population.

A factor of 3 was used to account for extrapolating from a subchronic study to chronic exposure scenarios (UF_S). Subchronic oral studies in both male and female rats and mice identify the liver as a critical target of bromobenzene toxicity. A subchronic inhalation study in mice provides supporting evidence for the hepatotoxicity of bromobenzene. There are no chronic exposure studies for bromobenzene, but results of chronic exposure to chlorobenzene indicate that the subchronic and chronic dose-responses are similar (see Section 5.1.2.3). It is reasonable to expect the subchronic and chronic dose-responses from exposure to bromobenzene to be similar as well.

An UF for extrapolation from a LOAEL to NOAEL (UF_L) was not needed because the current approach is to address this extrapolation as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR of a 10% increase in the incidence of cytomegaly was selected under an assumption that it represents a minimal biologically significant change.

A 10-fold UF was used to account for database deficiencies (UF_D). Subchronic studies in rats and mice are available. Developmental toxicity and multi-generation reproductive toxicity studies are lacking. Bromobenzene and chlorobenzene exhibit similarities in structure, toxicokinetic properties, and critical target of toxicity (liver) in rats and mice (see Section 4.5.4 for a detailed discussion). Therefore, the toxicity database for chlorobenzene was assessed for its potential to address database deficiencies for bromobenzene. For example, in a two-generation reproductive toxicity study in rats, chlorobenzene did not elicit any signs of reproductive toxicity in either generation at an exposure level of 450 ppm (Nair et al., 1987). In the same study, both F0 and F1 male rats exhibited chlorobenzene-induced hepatotoxicity from inhalation exposure at concentrations as low as 150 ppm. Chlorobenzene did not induce developmental effects in the fetuses of pregnant rats exposed to vapor concentrations as high as 590 ppm for 6 hours/day on gestation days 6-15 (John et al., 1984) (IBT, 1977). However,

reproductive effects, in particular multi-generational effects, may be important to informing the bromobenzene toxicity database considering the high DNA reactivity of this chemical. Bromobenzene was second only to 1,2 dibromoethane in its relative in vivo reactivity with rat liver DNA, exhibiting higher reactivity than 1,2-dichloroethane, chlorobenzene, epichlorohydrin, and benzene (Prodi et al., 1986). Therefore, the lack of a multi-generational study is of particular concern because genetic damage to germ cells of an F1 generation may not be detected until the F2 generation. In the absence of any information concerning reproductive and developmental endpoints following bromobenzene exposure, an UF of as applied.

I.B.2.4. ADDITIONAL STUDIES/COMMENTS

Additional studies/comments for the subchronic inhalation RfC (see Section I.B.1.4) apply to the derivation of the chronic inhalation RfC.

I.B.2.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study — Medium
Data Base — Low-to-Medium
RfC — Low-to-Medium

The overall confidence in the chronic RfC is low-to-medium. Due to a low number of animals per treatment group (10/group), the confidence in the principal study is medium. Confidence in the database is low-to-medium. Studies assessing the developmental toxicity and multi-generation reproductive toxicity of bromobenzene are lacking.

I.B.3. EPA DOCUMENTATION AND REVIEW OF THE SUBCHRONIC AND CHRONIC INHALATION RfC

Source Document — U.S. EPA. (2009).

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to the EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Bromobenzene* (U.S. EPA, 2009).

I.B.4. EPA CONTACTS

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 (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Bromobenzene
CASRN — 108-86-1
Section II. Last Revised — 09/30/2009

This section 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 and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

This is the first IRIS assessment for bromobenzene. No carcinogenicity assessment was previously available on IRIS.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

No information is available on the carcinogenicity of bromobenzene in humans.

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), there is "*inadequate information to assess the carcinogenic potential*" of bromobenzene. No human data or animal cancer bioassays are available for bromobenzene.

II.A.2. HUMAN CARCINOGENICITY DATA

No relevant human data are available.

II.A.3. ANIMAL CARCINOGENICITY DATA

No relevant animal data are available.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Bromobenzene was not mutagenic in the Ames assay (Nakamura et al., 1987; Rosenkranz and Poirier, 1979; Simmon, 1979; Simmon et al., 1979; McCann et al., 1975) and did not consistently produce marked cytogenetic effects *in vitro* with mammalian cells, even in the presence of rat liver S-9 preparations (Galloway et al., 1987; Pienta et al., 1977). Bromobenzene induced micronuclei in bone marrow of mice given acute oral doses of 125 mg/kg (Mohtashamipur et al., 1987) and was bound to DNA and RNA following intraperitoneal injection (Prodi et al., 1986; Colacci et al., 1985). Bromobenzene was second only to 1,2 dibromoethane in its relative in vivo reactivity with rat liver DNA, exhibiting higher reactivity than 1,2-dichloroethane, chlorobenzene, epichlorohydrin, and benzene (Prodi et al., 1986).

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

Not applicable.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document — U.S. EPA. (2009)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to the EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Bromobenzene* (U.S. EPA, 2009). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

II.D.2. EPA REVIEW

II.D.3. EPA CONTACTS

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 (email address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Bromobenzene
CASRN — 108-86-1

VI.A. SUBCHRONIC AND CHRONIC ORAL RfD REFERENCES

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VI.B. SUBCHRONIC AND CHRONIC INHALATION RfC REFERENCES

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VII. REVISION HISTORY

Bromobenzene
CASRN — 108-86-1
File First On-Line — 09/30/2009

Date	Section	Description
09/30/2009	I., II.	File first on-line.

VIII. SYNONYMS

Bromobenzene
CASRN — 108-86-1
Section VIII. Last Revised — 09/30/2009

- 108-86-1
- 1-Bromobenzene
- Bromobenzol
- C6H5Br
- Monobromobenzene
- NCI-C55492
- Phenyl bromide
- UN2514