1,2-Dibromoethane; CASRN 106-93-4

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 1,2-DIBROMOETHANE

File First On-Line 09/07/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/29/2004
Inhalation RfC (I.B.)	yes	07/29/2004
Carcinogenicity Assessment (II.)	yes	07/29/2004

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 1, 2-Dibromoethane
CASRN — 106-93-4
Section I.A. Last Revised — 07/29/2004

In general, the oral Reference Dose (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. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis and 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. Since 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.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	RfD
Testicular atrophy, liver peliosis, and adrenal cortical degeneration **Rat chronic oral gavage study, NCI, 1978**	LOAEL: 27 mg/kg-day	3000	9 E-3 mg/kg-day

* Conversion Factors and Assumptions: Adjustment of the LOAEL for intermittent exposure of 5 days/week (38 mg/kg-day x 5/7) results in a daily dose of 27 mg/kg-day.

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

National Cancer Institute (NCI). (1978) Bioassay of 1,2-dibromoethane for possible carcinogenicity. Bethesda, MD: National Cancer Institute. NTIS no. PB 288428.

In an NCI (1978) study, 50 Osborne-Mendel rats/sex/group were administered 1,2-dibromoethane in corn oil by gastric intubation. The initial doses utilized for male and female rats were 40 and 80 mg/kg-day. However, high treatment-related mortality (18/50 males and 20/50 females) caused a discontinuation in the intubation of the high-dose group after treatment in week 16. Intubation of this group was suspended for 13 weeks and then restarted at week 30 at which time the surviving rats received the low-dose regimen. All surviving male and female rats in both dosage groups were sacrificed at weeks 49 and 61, respectively. Time-weighted average low- and high-doses were 38 and 41 mg/kg-day for male rats, and 37 and 39 mg/kg-day for female rats. The authors reported that necropsy was performed on each animal whether it died, was sacrificed while moribund, or at the end of the study. Incidence data was reported for all animals necropsied, regardless of when they died or were sacrificed.

Among male rats, liver peliosis was observed in 0/40 control, 10/50 low-dose, and 9/50 high-dose groups. Among female rats, peliosis was observed in 0/40 control, 4/47 low-dose, and 2/48 high-dose groups. Peliosis is marked by engorgement of the liver with blood due to blockage of the lumen of the sinus or destruction of the epithelial wall of the sinusoid and is

not considered to be a precursor to liver cancer. Although hepatocellular carcinomas were detected in 5/48 female rats, the increase was not statistically significant. No increases in hepatocellular tumors were detected in males. Squamous cell tumors found in the liver were the result of metastases from forestomach tumors.

Another co-critical endpoint in this study is the induction of testicular atrophy. The incidence of atrophy was reported in 0/20 vehicle controls sacrificed after 61 weeks, 14/49 low-dose (38 mg/kg-day) group sacrificed after 49 weeks, and 18/50 high-dose group (41 mg/kg-day) sacrificed after 49 weeks. Testicular atrophy was also noted in 11/20 untreated control rats sacrificed at 107 weeks. Testicular atrophy in the latter group was likely to be age related, because it was not seen in 61 week controls and the duration was much longer than for exposed rats. The 61 week vehicle controls are therefore considered to be the appropriate control group

Although tumors of the tunica vaginalis, the serous covering of the testes, were reported in the NCI (1978) study, testicular atrophy is not considered a precursor to this effect. The tunica albuginea, a dense, fibrous membrane lies between the testis and the tunica vaginalis. Thus, the tunica vaginalis is neither in direct contact with the testes, nor is it composed of structurally or functionally related tissue. The reported testicular effects can, therefore, be considered a noncarcinogenic endpoint separated from nearby tunica vaginalis tumors.

Testicular effects were also reported in bulls administered oral doses of 2-4 mg/kg 1,2-dibromoethane (Amir and Ben-David, 1973; Amir and Volcani, 1965, 1967). These studies were not selected for RfD development because of the small numbers of animals and the use of one exposure level and because bulls are ruminants with a significantly different physiology. However, these bull studies provide supporting evidence for testicular effects of 1,2-dibromoethane at similar doses, after allometric adjustment[1], as those used in the NCI (1978) study.

A third co-critical endpoint, was adrenal cortical degeneration (0/40 controls, 13/48 low-dose group, and 9/47 high-dose group) in the male Osborne-Mendel rats of the NCI (1978) study. A similar effect was observed in the female rats (1/40 controls, 3/44 low-dose, and 8/45 high-dose animals) of this study and female F344 rats of the NTP (1982) chronic inhalation study. NCI (1978) reported an increased incidence of adrenal tumors in female Osborne-Mendel rats following oral exposure, and Wong et al. (1982) identified an increased incidence of adrenal tumors in both male and female Sprague-Dawley rats following inhalation exposure. However, adrenal tumors were not observed in male Osborne-Mendel rats of the NCI (1978) oral study and were not observed in the F344 rats of either sex in the NTP (1982) inhalation study. Thus, a clear association between this degenerative effect and adrenal tumors cannot be established, and use of this endpoint in support of a noncancer RfD is deemed appropriate.

RfDs can be derived by either development of a benchmark dose or through determination of a NOAEL or a LOAEL. TWA doses for male and female rats of the NCI (1978) study were very similar, but a higher incidence and severity of effects were observed in male rats at the low dose. Adjustment of the lower time weighted average low dose for intermittent exposure of 5 days/week (38 mg/kg-day x 5/7) results in a LOAEL of 27 mg/kg-day. The adjusted daily dose of 27 mg/kg-day can be considered a LOAEL for peliosis (20% response), testicular atrophy (29% response), and adrenal cortical degeneration (27% response). Because testicular atrophy occurs with high incidence in aged untreated rats, the lack of testicular atrophy in the vehicle control group at 61 weeks suggests that 1,2-dibromoethane hastens the onset of testicular atrophy.

A benchmark dose analysis was performed for all three of the co-critical endpoints and is described in Appendix B of the toxicological review for this assessment (U.S. EPA, 2004). This analysis was done using both the initial, unadjusted doses of 40 and 80 mg/kg-day and time weighted average (TWA) doses reported by the authors. Because the peliosis and adrenal cortical degeneration effects occurred at a much greater incidence towards the end of the study, the BMD assessments which used time weighted average doses may be more appropriate for these endpoints. However, because the incidence of testicular atrophy was similar at the beginning, middle and end of the study (6/20 at 9-24 wks; 4/10 at 25-39 weeks; 4/9 at 40-44 wks and 4/11 at 45-49 weeks) the dose rate may be more critical to the occurrence of this effect. However, there is not enough data to make a definitive determination in this regard. Depending on whether unadjusted or TWA doses were used, $BMDL_{10}$ estimates for these three endpoints ranged from approximately 7-10 mg/kg-day. Because of high mortality and unusual dosing in the high dose group, there is a great deal of uncertainty associated with these BMD results and they are only provided here in support of the NOAEL/LOAEL approach.

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[1]The allometric adjustment refers to the scaling of doses between species according to body mass raised to the 3/4 power, which the Agency has endorsed for carcinogens. The presumption of this adjustment is that equal doses in these units (i.e., $mg/kg^{3/4}$-day) when administered daily over a lifetime, will result in equal risk across mammalian species (U.S. EPA, 2002). The bulls were assumed to weigh 1000 kg (Amir, 1975). After allometric adjustment, the doses given to the NCI (1978) male rats were less than 2 times, and therefore similar to, the doses given to the Amir and Volcani (1965; 1967) bulls (11 vs 21 $mg/kg^{3/4}$-day).

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

UF = 3,000. Uncertainty factors of 10 for interspecies variability, 10 for intraspecies variability in sensitivity, and 10 for adjustment from a LOAEL to a NOAEL were assigned, as there was no information available that suggested other values were appropriate. A subchronic to chronic uncertainty factor was not considered necessary because all animals of the low-dose group were continuously exposed for approximately one year.

A 10-fold uncertainty factor accounting for the extent and quality of the database was deemed necessary due primarily to the poor quality of the principal study, the lack of high quality developmental and reproductive studies by the oral route of exposure, and limited studies in bulls that suggest adverse effects on sperm at low doses. High mortality in the principal study (NCI, 1978) causes considerable uncertainty with respect to the exposures that the animals received and the responses that might have been observed had the animals survived to term. The lack of a multigeneration study is also of concern in light of the genotoxicity of 1,2-dibromoethane, because any genetic damage to the germ cells of the F1 generation would not be detected until the F2 generation. Developmental toxicity studies covering major organogenesis (but not studies covering the entire period of gestation) are available in two species via the inhalation route, and inhalation systemic toxicity studies that evaluated the respiratory tract are available in two species. There is also some limited evidence for neurobehavioral developmental effects caused by 1,2-dibromoethane as well as endocrine disruption (based on effects on other endocrine organs as well as changes in hormone levels).

This results in an overall uncertainty factor, $UF_{(Total)}$, of 10,000. In general, the individual uncertainty factors that comprise the $UF_{(Total)}$ are expected to be conservative with respect to the behavior of the average chemical (Dourson and Stara, 1983). For this reason, the Agency recommended maximum uncertainty factor of 3000 (U.S. EPA, 2002; U.S.EPA, 1994) has been applied.

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

The only human data available concerning the effects of oral exposure to 1,2-dibromoethane are from case reports of suicides. However, inhalation studies in humans (Ratcliffe et al., 1987) and several oral studies in rodents (NCI, 1978) and bulls (Amir and Ben-David, 1973; Amir and Volcani, 1965, 1967; Amir, 1973, 1975; Amir and Lavon, 1976; Amir et al., 1977) have been shown to adversely affect male reproductive endpoints. When 1,2-dibromoethane was administered orally to bulls at doses that did not affect the growth or health of the animals, it was shown to adversely affect various sperm parameters. Adverse effects included altered sperm morphology, decreased motility, and depleted sperm from seminiferous tubules. In addition, the spermicidal effect of 1,2-dibromoethane occurs during spermatogenesis,

indicating that the effect is not direct. Overall, the data indicate that 1,2-dibromoethane is a male reproductive toxicant in animals.

Animal studies have also demonstrated other noncancer effects in rats and mice after subchronic- and chronic-duration oral and inhalation (see section I.B.) exposure to 1,2-dibromoethane. Excessive mortality, weight gain depression, testicular atrophy, forestomach lesions, and liver and adrenocortical degeneration were reported in rats and mice after long-term oral exposure to 1,2-dibromoethane (NCI, 1978). The systemic effects associated with long-term oral exposure are generally consistent with those resulting from inhalation dosing.

The mechanism of 1,2-dibromoethane-mediated cytotoxicity has been studied in isolated rat hepatocytes (Khan et al., 1993). It was demonstrated that microsomal cytochrome P 450-dependent oxidative metabolism of 1,2-dibromoethane produces the metabolite 2-bromoacetaldehyde. The results suggest that the cytotoxic mechanisms for 1,2-dibromoethane may possibly be attributed to lipid peroxidation and/or protein binding induced by 2-bromoacetaldehyde. In addition, the study authors considered that the conjugation of 1,2-dibromoethane with GSH may also contribute to cytotoxicity. Botti et al. (1982, 1986, 1989a, 1989b) and Masini et al. (1986) provided evidence that 1,2-dibromoethane-induced depletion of hepatic mitochondrial GSH correlated with hepatotoxicity and perturbations in mitochondrial Ca^{2+} homeostasis.

The results of *in vitro* and *in vivo* experiments suggest that the renal toxicity of 1,2-dibromoethane may be due to its biotransformation by GSH conjugation followed by further conversion in the kidney to highly reactive metabolites (Novotna and Duverger-van Bogaert, 1994). Repeated administration of 1,2-dibromoethane to rats has been shown to enhance the content of GSH in the liver and kidney (Mann and Darby, 1985). It has been suggested that lipid peroxidation may play a role in the 1,2-dibromoethane-induced pathogenesis of liver cell necrosis (Albano et al., 1984).

The metabolite 2-bromoacetaldehyde is formed during the oxidative metabolism of 1,2-dibromoethane and undergoes conjugation with GSH (Wong et al., 1982). Disulfiram inhibits aldehyde dehydrogenase and may alter the metabolism of 1,2-dibromoethane by preventing the further metabolism or conjugation of 2-bromoacetaldehyde. It has been suggested that, because disulfiram is used to treat alcoholics, these individuals may be at a greater risk to 1,2-dibromoethane toxicity (Wong et al., 1982). Disulfiram has been reported to enhance the carcinogenicity of 1,2-dibromoethane (Elliott and Ashby, 1980).

There are no human studies indicating that children are more susceptible than adults to the toxic effects of 1,2-dibromoethane. However, there is evidence in mice that fetal epithelia can bind ^{14}C-1,2-dibromoethane nonvolatile metabolites after i.v. injection to pregnant animals in

different stages of gestation (Kowalski et al., 1986). High-level binding was observed in the oral epithelium, nasal mucosa, and forestomach. These results suggest that fetuses are likely to be exposed to 1,2-dibromoethane from maternal circulation. The embryotoxic potential of 1,2-dibromoethane to humans has been suggested by the results of an *in vitro* study with cultured rat embryos in which it was shown that bioactivation of 1,2-dibromoethane by GST induced manifestations of embryotoxicity (Mitra et al., 1992). Although oral data on reproductive/developmental effects are very limited, some indication of doses that might cause these effects can be obtained from gavage studies in bulls and inhalation studies in rats and mice (section I.B).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — Low to Medium
Database — Low to Medium
RfD — Low to Medium

Confidence in the study utilized to derive the RfD is low to medium. Although the critical study was of chronic duration and involved a large number of animals, high mortality, close dose spacing, and the absence of a NOAEL made this study difficult to assess. Confidence in the oral database is also considered to be low to medium. Although oral data on reproductive/developmental effects are very limited, some indication of doses that might cause these effects can be obtained from gavage studies in bulls and inhalation studies in rats and mice. The overall confidence in the RfD is considered to be low to medium.

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 (2004)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of 1, 2-Dibromoethane (U.S. EPA, 2004). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***

Agency Completion Date -- 07/26/2004

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 (email address).

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

Substance Name — 1,2-Dibromoethane
CASRN — 106-93-4
Section I.B. Last Revised — 07/29/2004

In general, the Reference Concentration (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. 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 likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis.

Inhalation RfCs are derived according to the *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Since 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.

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	RfC
Nasal inflammation	$BMCL_{10}$(HEC): 2.8 mg/m^3	300	9 E-3 mg/m^3

Critical Effect	Experimental Doses*	UF	RfC
Mouse chronic inhalation study, NTP, 1982			

*Conversion Factors and Assumptions: 1,2-Dibromoethane is considered a Category 2 gas because it is relatively insoluble in water and demonstrates systemic toxicity. For Category 2 gases, HEC values are calculated using methods for Category 1 gases for portal-of-entry effects and Category 3 methods for systemic effects (U.S .EPA, 1994). In Table 1, the EPA RfC method for Category 3 gases was used to derive $BMDL_{10}$(HEC)s for the liver, testicular, retinal, adrenal, and splenic effects, and the method for Category 1 gases was used to derive $BMDL_{10}$(HEC) for nasal effects[2]. The NTP (1982) data for nasal inflammation in female mice resulted in the lowest $BMDL_{10}$(HEC) of 2.8 mg/m^3 1,2-dibromoethane. Assuming a temperature of 25°C, a barometric pressure of 760 mm Hg, and a molecular weight for 1,2-dibromoethane of 187.88, one ppm equals 7.68 mg/m^3 (187.88/24.45). Application of the multistage model from EPA Benchmark Dose Software (BMDS) version 1.3.2, resulted in an estimated $BMDL_{10}$ of 80.1 mg/m^3 for nasal inflammation in female mice. Adjustment to continuous exposure (30/168 hours/week) results in a duration adjusted $BMDL_{10}$(ADJ) of 14.3 mg/m^3. The $BMDL_{10}$(HEC) was calculated for an effect in the extrathoracic (ET) region. Minute $volume_{mouse}$ = 0.041 L/min, minute $volume_{human}$ = 13.8 L/min, surface $area(ET)_{mouse}$ = 3 cm^2, surface $area(ET)_{human}$ = 200 cm^2. Regional gas dose ratio(ET) = [minute $volume_{mouse}$/surface $area(ET)_{mouse}$]/[minute $volume_{human}$/surface $area(ET)_{human}$] = 0.198. $BMDL_{10}$(HEC) = $BMDL_{10}$(ADJ) x regional gas dose ratio(ET) = 14.3 mg/m^3 x 0.198 = 2.8 mg/m^3.

[2] An excess risk of 10% has generally been the default benchmark response (BMR) level for quantal data because it is at or near the limit of sensitivity in most bioassays. The Agency's benchmark dose technical guidance (U.S.EPA, 2000) does indicate that a lower BMR can be used if a study has "greater than usual sensitivity." However, this study cannot be said to have greater than usual sensitivity because it involves only two dose groups and high mortality in all dose groups. In addition, low-dose responses were at or above 10% for all endpoints.

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

NTP (National Toxicology Program). (1982) Carcinogenesis bioassay of 1,2-dibromoethane (CAS No. 106-93-4) in F344 rats and $B6C3F_1$ mice (inhalation study). NTP-80-28, NIH

publication no. 82-1766; Available from National Technical Information Service, Springfield, VA; PB82-181710.

The National Toxicology Program (NTP) (1982) performed an inhalation carcinogenicity bioassay in rats and mice. Male and female Fischer 344 rats and $B6C3F_1$ mice (n=50 per sex, species, and exposure group) were exposed to 0, 10, or 40 ppm (0, 77, or 307 mg/m^3) 1,2-dibromoethane for 6 hr/day, 5 days/week. The study was designed to assess potential adverse effects of 1,2-dibromoethane following 103 weeks of exposure. However, high-exposure rats of both sexes and female mice exhibited high mortality (84-90%) beginning at about 60 weeks, resulting in early termination (between 78 and 91 weeks) of these exposure groups. The low exposure groups were not terminated until the end of the study (104-106 weeks) though low-exposure female mice displayed high mortality (62%) relative to controls (20% mortality). The male mouse study was not considered as relevant for derivation of an RfC because of high mortality in control and exposed groups due to complications from urinary tract infections that were not exposure-related.

The noncarcinogenic effects observed in the NTP (1982) are hepatic necrosis (male and female rats), testicular degeneration (male rats), retinal atrophy (female rats), adrenal cortical degeneration (female rats), splenic hematopoiesis (female mice), and inflammation of the nasal cavity (female mice). The critical liver endpoint differs somewhat from that which was used to develop the oral RfD (peliosis). They are, however, both measures of liver toxicity and are likely to be closely related. Because liver cancer induction was not statistically significantly increased in either sex following inhalation exposure to 1,2-dibromoethane, and because necrosis is not considered a necessary precursor to induction of liver cancer, necrosis is considered to be a suitable endpoint for quantifying the noncancer effects of 1,2-dibromoethane.

Because the NTP study demonstrated adequate spacing of exposure levels with increasing responses at increasing exposure levels, the inhalation toxicity of 1,2-dibromoethane was evaluated using benchmark dose (BMD) analysis. To derive an RfC, the BMDL values derived from the NTP (1982) study were adjusted to equivalent continuous exposures, converted to human equivalent concentrations (HECs), and then divided by uncertainty factors. For systemic (liver, testicular, retinal, adrenal, and splenic) effects, the EPA RfC method for Category 3 gases (U.S. EPA, 1994) was used to convert BMDLs to BMDL(HEC)s. The EPA RfC method for Category 1 gases was used to convert the BMDL for nasal effects to a BMDL(HEC). As shown in Table 1, the NTP (1982) data for nasal effects in female mice resulted in the lowest BMDL(HEC) of 2.8 mg/m^3. This BMDL(HEC) was then divided by an overall uncertainty factor of 300 (discussed below) to obtain the RfC of 9 E-3 mg/kg-day.

Table 1. HEC estimates

	Male Rats		Female Rats			Female Mice	
	Hepatic necrosis (mg/m^3)[a]	**Testicular degeneration (mg/m^3)**	**Hepatic necrosis (mg/m^3)**	**Adrenal cortical degeneration (mg/m^3)**	**Retinal atrophy (mg/m^3)**	**Splenic hematopoiesis (mg/m^3)**	**Nasal inflammation (mg/m^3)**
NOAEL	NA	NA	NA	NA	NA	NA	NA
LOAEL	76.8	76.8	76.8	76.8	76.8	76.8	76.8
BMDS model[b]	Probit	LogLogistic	LogProbit	LogLogistic	LogLog	LogLogistic	LogProbit
BMD_{10}	131.774	53.2579	172.374	124.823	125.806	59.554	102.192
$BMDL_{10}$	105.343	35.0725	122.02	66.495	105.41	40.2456	80.1088
$BMDL_{10}$ (ADJ)[c]	18.8	6.3	21.8	12.0	18.8	7.2	14.3
$BMDL_{10}$ (HEC)[d]	18.8	6.3	21.8	12.0	18.8	7.2	2.8

[a]Assuming a temperature of 25°C, a barometric pressure of 760 mm Hg, and a molecular weight for 1,2-dibromoethane of 187.88, one ppm equals 7.68 mg/m^3 (187.88/24.45).

[b]In accordance with EPA draft guidance (U.S. EPA, 2000) the selected models were chosen on the basis of goodness of fit criteria (AIC and chi-square residual values) and visual inspection.

[c]Adjustment to continuous exposure involved multiplying the BMDL by 5 d/7 d x 6 hr/24 hr.

[d]HEC values were calculated in accordance with EPA (1994) RfC methods. For extrarespiratory effects, a default adjustment factor of 1.0 was used for adjusting from ADJ to HEC values because 1,2-dibromoethane blood:air partition coefficients are not known for the experimental species and humans. For the respiratory effect (nasal inflammation) the HEC was calculated for an effect in the extrathoracic (ET) region. Minute $volume_{mouse}$ = 0.041 L/min, minute $volume_{human}$ = 13.8 L/min, Surface $area(ET)_{mouse}$ = 3 cm^2, Surface $area(ET)_{human}$ = 200 cm^2. Regional gas dose ratio(ET) = [minute $volume_{mouse}$/surface $area(ET)_{mouse}$]/[minute

$volume_{human}/surface\ area(ET)_{human}$] = 0.198. BMDL(HEC) = BMDL(ADJ) x regional gas dose ratio(ET) = 14.3 mg/m^3 x 0.198 = 2.8 mg/m^3.

Sources: NTP, 1982; U.S. EPA, 2004.

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

UF = 300. Uncertainty factors of 3 for interspecies variability, 10 for intraspecies variability in sensitivity, and 10 for database uncertainty were assigned. An uncertainty factor of 3 was applied for interspecies pharmacodynamics as a consequence of considering human equivalent dosimetry and due to the lack of data suggesting a more or less divergent response in humans. An uncertainty factor of 10 for intraspecies variability in sensitivity results was applied as well as a default value due to the lack of data indicating a different degree of variability in humans.

An uncertainty factor for less than lifetime exposure is considered to be unnecessary because the principal study was carried out for at least 88 weeks. A database uncertainty factor of 10 is applied. High mortality in the principal study (NTP, 1982) causes considerable uncertainty with respect to the exposures that the animals received and with respect to the responses that might have been observed has the animals survived to term. A 1-generation inhalation reproductive toxicity study is available, but no multi-generation study. The lack of the multi-generation study is of particular concern in light of the genotoxicity of 1,2-dibromoethane, because any genetic damage to the germ cells of the F1 generation would not be detected until the F2 generation. Furthermore, the absence of an evaluation of sperm in reproductive toxicity study is of concern, in light of the effects observed in humans and bulls. Developmental toxicity studies covering major organogenesis (but not studies covering the entire period of gestation) are available in two species via the inhalation route, and inhalation systemic toxicity studies that evaluated the respiratory tract are available in two species. There is also some limited evidence for neurobehavioral developmental effects caused by 1,2-dibromoethane as well as endocrine disruption (based on effects on other endocrine organs as well as changes in hormone levels).

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

The limited epidemiological studies pertaining to subchronic and chronic effects from inhalation exposures focused primarily on reproductive and cytogenetic endpoints. The human data suggest that 1,2-dibromoethane may be a male reproductive toxicant. Decreased sperm count, ejaculate volume, and motility, and abnormal sperm morphology have been reported in workers following long-term inhalation exposure to 1,2-dibromoethane (Ratcliffe et al., 1987). Workers exposed to 1,2-dibromoethane for 6 weeks displayed decreased sperm velocity and volume (Schrader et al., 1988). Additionally, male workers in a plant manufacturing 1,2-

dibromoethane exhibited a significant decrease in fertility (Wong et al., 1979). However, the limitations of these studies (inadequate exposure data, potential exposure to other reproductive toxicants, moderate-to-extensive dermal exposure potential, and other confounding factors) render any interpretation of the evidence regarding the potential of inhaled 1,2-dibromoethane to induce reproductive effects in humans inconclusive.

The evidence that inhaled 1,2-dibromoethane is associated with reproductive and developmental effects in laboratory animals is incontrovertible. Reproductive and developmental effects have been reported in rats and mice following inhalation exposure (Short and Winston, 1979; Short et al., 1978). Effects in male rats included decreased testicular weight, decreased serum testosterone levels, testicular atrophy, and impairment of reproductive performance. Testicular atrophy has also been observed in male mice. Reported developmental effects in rats and mice consisted of decreased fetal body weight, increased resorptions, decreased fetal survival, and/or skeletal anomalies; however, these reproductive and developmental effects occurred at doses associated with significant toxicity and/or mortality in parental/maternal animals.

Other noncancer effects observed in rats and mice after chronic inhalation exposure to 1,2-dibromoethane include early mortality, depression of body weight gain, and nonneoplastic lesions of the respiratory system, liver, kidney, testis, eye, and adrenal cortex (NTP, 1982). Proliferative lesions of the nasal epithelium in mice have also been reported after chronic inhalation exposure to 1,2-dibromoethane (Stinson et al., 1981). It appears the respiratory system, particularly the nasal epithelium, is a target tissue following inhalation exposure in both species.

The results of a subchronic inhalation study in rats and mice revealed weight gain depression, swelling of adrenocortical cells, decreases in thyroid follicle size, and formation of megalocytic cells of the lining of bronchioles in rats and mice (NTP, 1982). In addition, Nitschke et al. (1981) reported elevated relative liver and kidney weights, focal epithelial hyperplasia of the nares, and diffuse respiratory hyperplasia. Similar respiratory effects were reported by Reznick et al. (1980), and Rowe et al. (1952) reported adverse liver and kidney effects in rats, guinea pigs, and monkeys. The subchronic toxicity data are generally consistent with reported chronic effects.

The mechanism of 1,2-dibromoethane-mediated cytotoxicity has been studied in isolated rat hepatocytes (Khan et al., 1993). It was demonstrated that microsomal cytochrome P 450-dependent oxidative metabolism of 1,2-dibromoethane produces the metabolite 2-bromoacetaldehyde. The results suggest that the cytotoxic mechanisms for 1,2-dibromoethane may possibly be attributed to lipid peroxidation and/or protein binding induced by 2-bromoacetaldehyde. In addition, the study authors considered that the conjugation of 1,2-

dibromoethane with GSH may also contribute to cytotoxicity. Botti et al. (1982, 1986, 1989a, 1989b) and Masini et al. (1986) provided evidence that 1,2-dibromoethane-induced depletion of hepatic mitochondrial GSH correlated with hepatotoxicity and perturbations in mitochondrial Ca^{2+} homeostasis.

The results of *in vitro* and *in vivo* experiments suggest that the renal toxicity of 1,2-dibromoethane may be due to its biotransformation by GSH conjugation followed by further conversion in the kidney to highly reactive metabolites (Novotna and Duverger-van Bogaert, 1994). Repeated administration of 1,2-dibromoethane to rats has been shown to enhance the content of GSH in the liver and kidney (Mann and Darby, 1985). It has been suggested that lipid peroxidation may play a role in the 1,2-dibromoethane-induced pathogenesis of liver cell necrosis (Albano et al., 1984).

The metabolite 2-bromoacetaldehyde is formed during the oxidative metabolism of 1,2-dibromoethane and undergoes conjugation with GSH (Wong et al., 1982). Disulfiram inhibits aldehyde dehydrogenase and may alter the metabolism of 1,2-dibromoethane by preventing the further metabolism or conjugation of 2-bromoacetaldehyde. It has been suggested that because disulfiram is used to treat alcoholics, these individuals may be at a greater risk to 1,2-dibromoethane toxicity (Wong et al., 1982). Disulfiram has been reported to enhance the carcinogenicity of 1,2-dibromoethane (Elliott and Ashby, 1980).

There are no human studies indicating that children are more susceptible than adults to the toxic effects of 1,2-dibromoethane. However, there is evidence in mice that fetal epithelia can bind ^{14}C-1,2-dibromoethane non-volatile metabolites after i.v. injection to pregnant animals in different stages of gestation (Kowalski et al., 1986). High-level binding was observed in the oral epithelium, nasal mucosa, and forestomach. These results suggest that fetuses are likely to be exposed to 1,2-dibromoethane from maternal circulation. The embryotoxic potential of 1,2-dibromoethane to humans has been suggested by the results of an *in vitro* study with cultured rat embryos in which it was shown that bioactivation of 1,2-dibromoethane by GST induced manifestations of embryotoxicity (Mitra et al., 1992).

It has been concluded that children's respiratory vulnerability is in part due to the fact that they have narrower airways than those of adults, and thus irritation that would produce only a slight response in an adult can result in potentially significant obstruction in the airways of a young child[3]. As such, the nasal inflamation effects of 1,2-dibromoethane may have a more significant health impact for infants and small children.

[3] *Ambient Air Pollution: Respiratory Hazards to Children* statement by the American Academy of Pediatrics, online at http://www.aap.org/policy/04408.html EXIT Disclaimer (also the

topic of the journal *Pediatrics*, Volume 92, No. 3, 1993, which could not be retrieved prior to this submission).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Confidence in the study used to derive the RfC is medium. The NTP (1982) inhalation study was well designed, using an adequate number of animals of both sexes, but was limited because of excessive mortality in the high-dose groups of both species, moderate mortality in low-dose female mice, and excessive mortality in male mice not related to 1,2-dibromoethane exposure. Confidence in the data base is medium. There are systemic inhalation toxicity studies in two species, one-generation (but no multigeneration) reproductive study, and developmental toxicity studies in two species that did not cover the full period of gestation. Although animal studies have shown that reproductive/developmental effects in females are likely to occur only at doses inducing maternal toxicity, the possibility remains that sperm quality may be adversely affected at lower doses. The overall confidence in this RfC assessment is medium.

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 (2004)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix A of the Toxicological Review of 1,2-Dibromoethane (U.S. EPA, 2004). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***

Agency Completion Date -- 07/26/2004

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 (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,2-Dibromoethane
CASRN — 106-93-4
Section II Last Revised — 07/29/2004

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 is described in the *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and both the central and upper bound estimates of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways (see Section II.B.1.) to better facilitate their use: (1) generally, the "oral slope factor" is the 95% upper bound on the estimate of risk per mg/kg-day of oral exposure; (2) the "drinking water unit risk" is the 95% upper bound on the estimate of risk, either per µg/L drinking water or per $\mu g/m^3$ air breathed; and (3) the 95% lower bound and central estimate on 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.

II.A. Evidence for Human Carcinogenicity

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

Under the *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), 2-dibromoethane is considered "likely to be carcinogenic to humans" based on strong evidence of carcinogenicity in animals and inconclusive evidence of carcinogenicity in an exposed human population. This weight-of-evidence carcinogenicity characterization replace the

previous classification of *B2; probable human carcinogen*, entered on IRIS on September 7, 1988. The new classification and slope factor estimates are based on a review of newer data and a reanalysis of the data used in the earlier assessment. This is based on the consistent findings of several studies reporting increased incidences of a variety of tumors in rats and mice of both sexes by different routes of administration at both the site of application and at distant sites, it can be concluded that there is strong evidence of the carcinogenicity of 1,2-dibromoethane in animals. The available evidence further supports a conclusion that 1,2-dibromoethane is a genotoxic carcinogen based on evidence from a variety of *in vitro* and *in vivo* test systems.

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

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Inadequate. Mortality of 161 workers occupationally exposed to 1,2-dibromoethane in two production facilities that were in operation from 1942-1969 and from the mid-1920s to 1976 has been investigated (Ott et al. 1980); the emphasis of the study was on cancer mortality and respiratory disease. Quantitative data from which to calculate an 8-hour time-weighted average (TWA) were not available for the first facility. However, an estimated TWA of 3.5 ppm was calculated for 1971-1972 and 5 ppm for the second facility. In the first facility, two deaths from malignant neoplasms were observed compared to 3.6 expected. In the second facility, 5 deaths were attributed to malignant neoplasms compared to 2.2 expected. The study is inconclusive in regards to 1,2-dibromoethane as a potential human carcinogen because of poor exposure assessment and co-exposure to other potential carcinogens.

II.A.3. Animal Carcinogenicity Data

Sufficient. 1,2-Dibromoethane has been tested for carcinogenicity by gavage and inhalation administration. NCI (1978) administered 1,2-dibromoethane by gavage to male and female Osborne-Mendel rats and $B6C3F_1$ mice. High mortality in both species in all exposure groups did not allow for dosing to a full 104 weeks. In addition, dosing adjustments were necessary as a result of high mortality. Male and female rats were sacrificed at weeks 49 and 61, respectively. Time-weighted average low and high doses were 38 and 41 mg/kg-day for male rats, and 37 and 39 mg/kg-day for female rats. All surviving male mice and high-dose female mice were sacrificed by week 78, while low-dose females were sacrificed at week 90. Low-dose females had a higher incidence of mortality compared to controls. Time-weighted

average low and high doses were 62 and 107 mg/kg-day, respectively, for mice of both sexes. In male rats, an increased incidence in forestomach squamous cell carcinoma, hemangiosarcoma, and thyroid follicular cell adenoma was observed. In addition to forestomach tumors and hemangiosarcomas, female Osborne-Mendel rats exhibited treatment-related hepatocellular and adrenocortical carcinoma at the high dose. In male and female $B6C3F_1$ mice, forestomach squamous cell carcinoma was the most common treatment-related cancer. Mice of both sexes also exhibited lung adenomas that were considered compound-related.

The carcinogenicity of 1,2-dibromoethane following oral administration is supported by a drinking water study (Van Duuren et al., 1985). Van Duuren et al. (1985) observed forestomach squamous cell carcinoma in male and female $B6C3F_1$ mice exposed to 4 mM 1,2-dibromoethane in drinking water for 15-18 months. Lung adenoma was not reported.

NTP (1982) exposed F344 rats and $B6C3F_1$ mice of both sexes to 0, 10, or 40 ppm (0, 77, or 307 mg/m3) 1,2-dibromoethane for 6 hr/day, 5 days/week. The study was designed to assess potential adverse effects of 1,2-dibromoethane following 103 weeks of exposure. However, high mortality in both species prompted early termination in some of the exposure groups. High-exposure male rats exhibited high mortality (90%), resulting in termination of that exposure group at week 88. Similarly, high-exposure female rats exhibited high mortality (84%) and were terminated at week 91. Mortality in control and low-exposure rats of both sexes were comparable, and terminal sacrifices were conducted at 104 weeks. Mortality was high in exposure and control groups of male mice, and all male mice were sacrificed at 78 weeks. The principal cause of mortality in male mice was ascending, suppurative urinary tract infection progressing to necrotic and ulcerative lesions around the urethral opening; chronic or suppurative cystitis; and ascending, suppurative pyelonephritis.

1,2-Dibromoethane-induced nasal cavity tumors in male and female Fischer 344 rats. Hemangiosarcoma was also demonstrated in high-dose animals of both sexes. In addition, mesothelioma of the tunica vaginalis, mammary fibroadenoma, and adenocarcinoma were observed in males and females, respectively. In female $B6C3F_1$ mice, a similar tumor pattern was observed compared to female rats. However, female mice displayed treatment-related alveolar/bronchiolar adenoma and carcinoma, lung/bronchiolar adenoma and carcinoma, and fibrosarcoma. Stinson et al. (1981) also reported carcinoma of the nasal cavity in female $B6C3F_1$ mice exposed to 40 ppm 1,2-dibromoethane by inhalation for 90 weeks. Benign squamous papilloma was also observed in male and female $B6C3F_1$ mice exposed to 40 ppm 1,2-dibromoethane. Mortality was not reported in this study and only the nasal cavities were examined.

Wong et al. (1982) reported an increase in liver, kidney, adrenal, subcutaneous, and thyroid cancers and hemangiosarcomas in male and female Sprague-Dawley rats exposed to 1,2-dibromoethane by inhalation.

II.A.4. Supporting Data for Carcinogenicity

1,2-Dibromoethane has been studied for mutagenic potential by a variety of *in vitro* and *in vivo* test systems and is a direct-acting mutagen in bacteria. 1,2-Dibromoethane was positive for *S. typhimurium* revertant strains TA1535, TA100, and TA98 (Barber et al., 1981) and induced point mutations in *S. typhimurium* strains TA1535 and TA100, *S. coelicolor*, and *A. nidulans* (Carere and Morpurgo, 1981). 1,2-Dibromoethane has been shown to induce chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells (Ivett et al., 1989; Tan and Hsie, 1981; Brimer et al., 1982; Ballering et al., 1998; Graves et al., 1996). 1,2-Dibromoethane has also been reported to induce gene mutations in two human lymphoblastoid cell lines, AHH-1 and TK6 (Crespi et al., 1985) and sister chromatid exchanges in human peripheral lymphocyte cultures (Tucker et al., 1984). *In vivo*, 1,2-dibromoethane induced DNA damage in rats following oral administration (Kitchin and Brown, 1986, 1987; Sasaki et al., 1998). Intraperitoneal administration of radiolabeled 1,2-dibromoethane has been shown to bind DNA in the liver, kidney, stomach, and lung of rats and mice (Arfellini et al., 1984), and S-[2-(N^7-guanyl)ethyl]glutathione has been identified as the major DNA adduct formed in rats following treatment with 1,2-dibromoethane (Kim et al., 1990; Koga et al., 1986).

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

II.B.1. Summary of Risk Estimates

II.B.1.1. Oral Slope Factor — 95% upper bound - 2×10^{0} $(mg/kg\text{-}day)^{-1}$
central tendency estimate - 1×10^{0} $(mg/kg\text{-}day)^{-1}$

II.B.1.2. Drinking Water Unit Risk — 95% upper bound* - 6×10^{-5} $(ug/L)^{-1}$
central tendency estimate - 3×10^{-5} $(ug/L)^{-1}$

***The upper bound and the central tendency estimates assume 2 L/day by a 70 kg human.**

II.B.1.3. Extrapolation Method

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	95% Upper Bound on Concentration Estimate
E-4 (1 in 10,000)	2 ug/L
E-5 (1 in 100,000)	2×10^{-1} ug/L
E-6 (1 in 1,000,000)	2×10^{-2} ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type - forestomach tumors, hemangiosarcomas, thyroid follicular cell adenomas or carcinomas
Test Species - rat/Osborne-Mendel, male
Route - gavage

Administered dose (mg/kg-day)	Human equivalent dose (mg/kg-day)	Adjusted tumor incidence using poly-3 procedure		
		Forestomach tumors	Hemangio-sarcomas	Thyroid follicular cell tumors
0	0	0/13 (0%)	0/13 (0%)	0/13 (0%)
38	7.8	45/50 (90%)	11/42 (26.2%)	5/29 (12.8%)
41	8.4	33/34 (97.1%)	4/23 (17.4%)	8/23 (36.4%)

Source: NCI, 1978

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

Doses were converted to human equivalent doses on the basis of (body weight)$^{3/4}$. An upper limit for each cancer slope factor was estimated by linear extrapolation from the lower confidence limit on dose at the point of departure. In order to convey the total amount of risk potentially arising from multiple tumor sites, the slope factors from the three tumor sites for male rats were summed using a statistically appropriate method. That is, an upper bound on cancer risk was estimated by adding the central tendency risk estimates and calculating an upper confidence limit on the sum, using an estimate of the variance pooled across the three slope factors. The resulting (upper bound) slope factor was adjusted for daily exposure by multiplying by 7 days/5 days and for lifetime exposure by dividing by (49 weeks/104 weeks)^{3}. The slope factor should not be used with exposures greater than 0.5 mg/kg-day. See the Support Document for more information (U.S. EPA, 2004).

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

The NCI (1978) used an adequate number of test animals and dose levels, and examined the proper toxicological endpoints. However, significant mortality was observed at all dose levels and the route of exposure, gastric intubation, was not the preferred method of oral exposure. Due to the early mortality, the study was terminated prior to 104 weeks and adjustments to the dosing regimen were made. This produced essentially only one dose group when doses were compared on a time-weighted-average basis. Both dose groups received less than chronic exposure.

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

II.C.1. Summary of Risk Estimates

II.C.1.1. Air Unit Risk

Inhalation Unit Risk, 95% upper bound - $6 \times 10^{-4} (ug/m^3)^{-1}$
central tendency estimate - $3 \times 10^{-4} (ug/m^3)^{-1}$

II.C.1.2. Extrapolation Method:

The multistage model was used to characterize a point of departure at the lower end of the data range, using the lower 95% confidence limit on dose associated with extra risk (adjusted for background) at the point of departure for linear extrapolation to lower doses.

Air Concentrations at Specified Risk Levels:

Risk Level	95% Upper Bound on Concentration
E-4 (1 in 10,000)	2×10^{-1} ug/m^3
E-5 (1 in 100,000)	2×10^{-2} ug/m^3
E-6 (1 in 1,000,000)	2×10^{-3} ug/m^3

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

Tumor Type — nasal cavity (includes adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma), hemangiosarcomas, mesotheliomas
Test animals — rat/Fischer 344, male
Route — inhalation

Administered concentration (ppm)	Equivalent continuous concentration (ppm)	Human equivalent continuous concentration (ppm)	Tumor incidence adjusted using poly-3* Procedure		
			Nasal tumors	Hemangio-sarcomas	Mesotheliomas
0	0	0	1/46 (2%)	0/46 (0%)	1/46 (2%)
10	1.8	0.36	39/45 (86%)	1/43 (2%)	8/43 (19%)
40	7.1	1.42	41/43 (95%)	15/28 (54%)	25/35 (71%)

*Poly-3 procedure involves adjusting each animal represented in the denominator by $(t/104)^3$, where t is the time of final sacrifice in a given dose group.
Source: NTP, 1982

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

The continuous concentrations averaged over 24 hours per day and 7 days per week, 10 x (6/24) x (5/7) = 1.8 ppm, and 40 x (6/24) x (5/7) = 7.1 ppm were used for the calculation of benchmark concentrations and inhalation cancer slope factors. In addition, EPA RfC methodology (U.S. EPA, 1994, 2002) was used to estimate human equivalent dose corresponding to the nasal (extra-thoracic) region. 1,2-Dibromoethane was considered a Category 1 gas for this analysis, due to its assumed portal-of-entry toxicity in this tissue. Assuming a temperature of 25°C, a barometric pressure of 760 mm Hg, and a molecular weight for 1,2-dibromoethane of 187.88, one ppm equals 7.68 mg/m^3 (187.88/24.45). Minute $volume_{rat}$ = 0.21 L/min, minute $volume_{human}$ = 13.8 L/min, surface $area(ET)_{rat}$ = 15 cm^2, surface $area(ET)_{human}$ = 200 cm^2. Regional gas dose ratio(ET) = [minute $volume_{rat}$/surface $area(ET)_{rat}$]/[minute $volume_{human}$/surface $area(ET)_{human}$] = 0.20. Each of the exposures adjusted for continuous exposure above were multiplied by the regional gas dose ratio of 0.20 to yield human equivalent exposure levels.

To convey the total amount of risk potentially arising from multiple tumor sites, the slope factors from the three tumor sites for male rats were summed using a statistically appropriate method. That is, an upper bound on cancer risk was estimated by adding the central tendency risk estimates and calculating an upper confidence limit on the sum, using an estimate of the variance pooled across the three slope factors. The unit risk should not be used with exposures greater than 0.023 mg/m^3. (See U.S. EPA, 2004 for more information).

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

The NTP (1982) study was well-designed, used an adequate number of test animals and dose levels, and examined the proper toxicological endpoints.

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

II.D.1. EPA Documentation

Source Documents -- U.S. EPA (2004)

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of

this assessment. A record of these comments is included in Appendix A of the Toxicological Review of 1, 2-Dibromoethane (U.S. EPA, 2004). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

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

Agency Completion Date -- 07/26/2004

II.D.3. EPA Contacts (Carcinogenicity Assessment

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

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

VI. Bibliography

Substance Name — 1,2-Dibromoethane
CASRN — 106-93-4

VI.A. Oral RfD References

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VII. Revision History

Substance Name — 1,2-Dibromoethane
CASRN — 106-93-4

Date	Section	Description
09/26/1988	II.	Carcinogen summary on-line
07/29/2004	I.A., I.B., II.	Added RfD and RfC asssessments, revised carcinogenicity.

VIII. Synonyms

Substance Name — 1, 2-Dibromoethane
CASRN — 106-93-4
Section VIII Last Revised — 07/29/2004

- 106-93-4
- dibromoethane
- 1,2-dibromoethane
- dibromoethane, 1,2-
- alpha,beta-dibromoethane
- ethylene bromide
- Ethylene dibromide
- glycol dibromide
- S-dibromoethane