INTERIM

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

1,2-DIBROMOETHANE

(CAS Reg. No. 106-93-4)

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

1,2-Dibromoethane is a heavy, colorless non-flammable liquid . It was used previously as a scavenger in leaded gasoline and as a pesticide fumigant mixture for soil, grain, and pests. Currently it is used as a chemical intermediate in various industries. The odor of 1,2-dibromoethane is described as chloroform-like, foul-smelling and pungent; the odor threshold is 10 ppm. Humans exposed to 1,2-dibromoethane in air experience eye irritation, upper and lower respiratory tract irritation and systemic effects involving the liver, kidney, and nervous system. The gastrointestinal tract and heart are also affected. Effects of exposure to lethal concentrations are manifested very quickly with death may occur in less than 3 days depending on the exposure conditions. Effects of exposure to non-lethal concentrations (eye, pharyngeal, and bronchial irritation, headache, depression, loss of appetite) rapidly resolve after termination of exposure. Epidemiologic studies on reproductive parameters in male workers occupationally exposed showed decreased sperm velocity and semen volume in workers after short-term exposure and decreased number of sperm/ejaculate, increased percentage of workers with low sperm count, decreased sperm viability and motility, and increased proportion of abnormal sperm after long-term exposure to 1,2-dibromoethane.

Studies in animals exposed to 1,2-dibromoethane by inhalation have shown effects in several species similar to those experienced by humans. Animals exposed to lethal concentrations show evidence of eye and upper and lower respiratory tract irritation and toxicity primarily involving the liver and kidney in most species (dog, rat, guinea pig, and rabbit) and the heart and gastrointestinal tract in dogs. Exposure of animals to non-lethal concentrations primarily affect the upper respiratory tract, liver and kidney. Data were not available for deriving the level of distinct odor awareness (LOA) for 1,2-dibromoethane.

In rats exposed to 50, 100, 200, or 800 ppm 1,2-dibromoethane, no adverse effects were associated with estimated exposure times of 420, 150, 42, and 6 minutes, respectively (Rowe et al., 1952). Higher exposure concentrations and times were associated with increased liver weight and slight histopathological changes in the liver. AEGL-1 values were derived from the estimated time (420 minutes or 7 hours) of exposure of rats to 50 ppm, which was the lowest concentration and the longest duration of exposure. Therefore, the point of departure (POD) for AEGL-1 derivation is 50 ppm for a 420-minute (7-hour) exposure. The total uncertainty factor is 10 (1 for interspecies sensitivity and 10 for intraspecies variability). An uncertainty factor of 1 for interspecies sensitivity was selected because the effects and mode of action of 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans. physiologically-based pharmacokinetic (PBPK) modeling indicated that uptake in rats exposed to 1,2-dibromoethane is about three times greater than that of humans, and rats produce about five times more active metabolites from the cytochrome P450 pathway (associated with cytotoxicity) than humans. The PBPK model also predicted that rats would produce about 80 times more glutathione-S-transferase (GST) metabolites than humans. The pronounced difference in metabolite production (pharmacokinetics) between rats and humans would overwhelm any difference in pharmacodynamics. An interspecies uncertainty factor of 1 is, therefore, justified. The rationale for selecting an uncertainty factor of 10 for intraspecies variability also is based on the human genetic variability associated with P450 and GST metabolism. Production of P450 metabolites ranges about two- to threefold and production of glutathione-S-transferase metabolites ranges about ten fold in humans. Therefore, an intraspecies uncertainty factor of 10 should account for the variability within the human population. The ten Berge et al. (1986) equation ($C^n \times t = k$) was used to extrapolate to all

exposure durations. The value of n = 1.6 was derived by regression analysis of the exposure concentrations and times associated with no adverse effects (Rowe et al., 1952).

AEGL-2 values were derived from an acute inhalation study by Rowe et al (1952). The investigators estimated that exposure of rats to 800 ppm for 9 minutes, 200 ppm for 1 hour, or 100 ppm for 4 hours would be associated with adverse effects, consisting of increased liver weight and slight histopathological changes in the liver (not further defined). These effects are below those defined as AEGL-2 effects (that is, irreversible effects or impaired ability to escape). The POD selected for AEGL-2 derivation is 100 ppm for a 4-hour (240-minute) exposure, the lowest concentration and the longest duration of exposure. The total uncertainty factor was 10. An uncertainty factor of 1 was applied for interspecies sensitivity and 10 for intraspecies variability. The rationales for selecting the uncertainty factors are the same as described for AEGL-1 derivation. The ten Berge et al. (1986) equation ($C^n \times t = k$) was used to extrapolate to all exposure durations. The value of n = 1.6 was derived by regression analysis of the exposure concentrations and time Rowe et al. (1952) associated with adverse effects.

No rats among groups of 20 died after exposure to 100 ppm 1,2-dibromoethane for 8.5, 12, or 16 hours and an observation period of 3 weeks. AEGL-3 values were derived using 100 ppm for 8.5 hours as the POD (Rowe et al. 1952) because the exposure duration approximates that for the 8-hour AEGL. The total uncertainty factor was 10 (1 for interspecies sensitivity and 10 for intraspecies variability. The rationales for selecting the interspecies and intraspecies uncertainty factors are the same as described for AEGL-1 and -2. The ten Berge et al. (1986) equation ($C^n \times t = k$) was used to extrapolate to all exposure durations. The value of n = 1.4 was derived by regression analysis of the LCt_{01} values associated with exposure concentrations of 200, 400, 800, and 1600 ppm (Rowe et al., 1952). The higher concentrations were not included because it appears that two different mechanisms of toxicity may be involved with deaths at the lower concentrations.

The AEGL values are summarized in the Table below:

S 1. Summary of AEGL Values

Classification	Exposure Duration					
	10-min	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint/Reference**
AEGL-1 (Nondisabling)	52 ppm (400 mg/m^3)	26 ppm (200 mg/m^3)	17 ppm (131 mg/m^3)	7.1 ppm (55 mg/m^3)	4.6 ppm (35 mg/m^3)	NOAEL for liver toxicity (Rowe et al., 1952)
AEGL-2 (Disabling)	73 ppm (562 mg/m^3)	37 ppm (285 mg/m^3)	24 ppm (185 mg/m^3)	10 ppm (77 mg/m^3)	6.5 ppm (50 mg/m^3)	Slight histopathological changes in the liver; no-effect-level for irreversible toxicity (Rowe et al., 1952)
AEGL-3 (Lethal)	170 ppm (1308 mg/m^3)	76 ppm (585 mg/m^3)	46 ppm (354 mg/m^3)	17 ppm (131 mg/m^3)	10 ppm (77 mg/m^3)	no effect level for lethality (Rowe et al. 1952)

References:

Rowe, V.K., H.C. Spencer, D.D. McCollister, R.L. Hollingsworth, and E.M. Adams. 1952. Toxicity of ethylene dibromide determined on experimental animals. *Archives of Industrial Hygiene and Occupational Medicine* 6:158-173.

Ten Berge, W.F.; Zwart, A.; Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. *Journal of Hazardous Materials*. 13:301-309.

1. INTRODUCTION

1,2-Dibromoethane is a heavy colorless non-flammable liquid. Physical and chemical properties of 1,2-dibromoethane are presented in Table 1. 1,2-Dibromoethane was used previously as a scavenger in leaded gasoline and as an agricultural fumigant mixture for soil, grain, and pests (Reid 2001, HSDB 2004). It is currently used as a chemical intermediate for the production of pharmaceuticals, dyes, polymers, and other chemicals and as a solvent (HSDB 2004). 1,2-Dibromoethane is manufactured from ethylene and bromine (HSDB, 2004).

The database for 1,2-dibromoethane consists of human case studies, anecdotal information on occupational exposures, and epidemiologic studies on reproductive toxicity and carcinogenicity. Animal data consist of an acute inhalation study and repeat exposure studies in multiple species from a single investigative group. In addition, developmental and reproductive studies, developmental neurotoxicity studies, chronic toxicity/carcinogenicity studies, and in vivo genotoxicity studies are available for evaluation for AEGL development. Several investigators have examined uptake, metabolism distribution, and excretion of inhaled 1,2-dibromoethane and developed predictions based on physiologically based pharmacokinetic (PBPK) models. These data are used for AEGL development, support of AEGL values, and rationale for uncertainty factors.

TABLE 1. Chemical and Physical Properties for 1,2 Dibromoethane

Parameter	Value	Reference
Synonyms	Ethylene dibromide, EDB	O'Neil et al. 2001, RTECS 2004
Chemical formula	$BrCH_2CH_2Br$	O'Neil et al. 2001
Molecular weight	187.86	O'Neil et al. 2001
CAS Reg. No.	106-93-4	RTECS 2004
Physical state	Heavy liquid or colorless liquid	Lewis, 1993, O'Neil et al. 2001
Solubility in water	0.43g/100mL H_2O, soluble in ethanol & ethyl ether; Miscible with most solvents & thinners	Reid 2001 Lewis 1993, O'Neil et al. 2001
Vapor pressure	11 mm Hg @ 25EC; 17.4 mm HG @ 30EC	O'Neil et al. 2001, Lewis 1993
Vapor density (air =1)	6.5	HSDB, 2004
Liquid density (water =1)	2.172 @ 25EC (25/4EC)	Reid 2001
Melting point	9.97EC	Reid 2001
Boiling point	131-132EC	O'Neil et al., 2001
Flammability limits	None	Reid 2001
Refractive index	1.53789/435337 @ 20/25EC	Reid 2001, Lewis 1993
Conversion factors	0.13 ppm = 1.0 mg/m^3 7.7 mg/m^3 = 1.0 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Two workers died after a combination of acute inhalation and dermal exposure to 1,2-dibromoethane; both had acute liver and renal failure (Letz et al. 1984). The first worker (31 years old) was exposed for approximately 45 minutes after entering a 28,000-L nurse tank that was used to temporarily store fertilizer mixtures containing 1,2-dibromoethane, and the second worker (46 years old) was exposed for 20-30 minutes while attempting to rescue the first worker. Neither worker wore protective breathing apparatuses or protective clothing. The first worker

began to feel ill and collapsed within 5 minutes after entering the tank. The first worker was intermittently comatose, vomited, and complained of burning eyes and throat; he became combative, incoherent, followed by lethargy, coughing, and diarrhea and reeked of a strong chemical odor that was noticeable after rescue, in the emergency room, and during autopsy. Clinical examination revealed conjunctival and pharyngeal inflammation, cyanotic nail beds, sinus tachycardia, hepatomegaly, abdominal tenderness, and erythema and blistering on trunk and legs in one or both patients. Clinical pathologic findings in one or both patients included elevated hematocrit, white cell count, serum chloride, blood glucose, lactic dehydrogenase, aspartate aminotransferase, creatinine phosphokinase, and pseudocholinesterase, severe metabolic acidosis, and progressive renal failure. Blood bromine levels were elevated to 830 mg/L in the first worker and up to 500 mg/L in the second. The first worker died 12 hours after exposure and the second worker died 64 hours after exposure.

Autopsy findings in one or both workers included pulmonary edema, cyanosis, severe acute passive congestion of the viscera and brain, and evidence of severe liver and kidney damage. Extensive tissue autolysis was observed particularly in the second worker. Bromide concentrations in postmortem blood samples were 24 mg/L in the first worker and 136 mg/L in the second worker. 1,2-Dibromoethane concentrations in postmortem tissue samples ranged from 1.6-3.6 Fg/g in skin tissue, 8 Fg/g in adipose tissue, and #0.5 Fg/g in brain tissue. 1,2-Dibromoethane was not detected in heart, liver, lung, spleen, or kidney, but bromine levels ranged from 8-248 mg/L in the same tissues and in gastric secretions. Air samples taken from inside the tank 20 hours after the accident ranged from 15-41 ppm (average = 28 ppm), and samples of liquid in the bottom of the tank ranged from 1-3% indicating that the workers were exposed to 1,2-dibromoethane by dermal contact in addition to inhalation.

Autopsy findings also included degeneration of the liver, kidney, and heart in a woman who died approximately 44 hours after inhaling a total of 70 g 1,2-dibromoethane mistakenly administered through a gauze mask instead of the anesthetic, ethylene bromide (Marmetschke 1910). 1,2-Dibromoethane was administered in aliquots of about 10 mL (22 g); however, the duration of administration was not reported. Multiple clinical signs were noted, including coughing during administration, dizziness after completion of administration and vomiting, burning sensation in the chest, diarrhea, restlessness, nervousness, breathing difficulty, thirst, abdominal pain, and uterine hemorrhaging (second day). The autopsy results also showed signs of upper respiratory tract irritation, extensive surface hemorrhaging, swollen pulmonary lymph nodes, and hemorrhaging in the mediastinum. Microscopic findings included fatty degeneration in heart muscle and liver cells.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

The odor of 1,2-dibromoethane has been described as chloroform like (Reid, 2001), foul-smelling and pungent (Kochmann, 1928), or sweetish (Lewis, 1993). The odor threshold reported by Ruth (1986) is 76.9 mg/m^3 (10 ppm). Data were not available for deriving the level of distinct odor awareness (LOA) for 1,2-dibromoethane.

2.2.2. Case Reports and Anecdotal Data

A worker was exposed repeatedly to unknown concentrations of 1,2-dibromoethane vapor for short periods each time (Kochmann 1928). The worker described the odor of the

substance as foul-smelling and pungent. Irritation of the conjunctiva and external swelling of the lower eyelids, swelling of the glands under the chin and angle of the jaw (salivary glands), paleness, and fatigue were described after the first exposure. After returning to work, the worker experienced conjunctivitis, pharyngeal and bronchial irritation, severe loss of appetite, headache, and depression. The symptoms rapidly resolved each time after cessation of exposure. Kochmann (1928) reported on a case of "subacute poisoning" due to inhalation exposure to 1,2-dibromoethane vapor and noted that 50 ppm could be dangerous to exposed humans.

Three episodes of exposure to 1,2-dibromoethane occurred at concentration believed to range from 100 to 200 ppm resulted in gastrointestinal discomfort, vomiting, and respiratory involvement for durations of 1 hour or less or to lower concentrations (e.g., 75 ppm) for longer durations (ACGIH 1991). According to Ott et al. (1980), an industrial hygienist noted that a strong odor and respiratory irritation occur when 1,2-dibromoethane concentrations reach 75 ppm, and that gastrointestinal discomfort and vomiting may also occur during acute exposure. Additional details were not provided in either report.

2.2.3. Epidemiologic Studies

Ott et al. (1980) conducted a study on the mortality experience of workers at two 1,2-dibromoethane manufacturing facilities. Plant No. 1 produced 1,2-dibromoethane from 1942 to 1969, and Plant No. 2 produced 1,2-dibromoethane from the mid-1920s to 1976. Personal and area monitoring data were available only for Plant No. 2. Reactor and still operators were routinely exposed to 1,2-dibromoethane and workers in other departments were occasionally exposed. 1,2-Dibromoethane concentrations for reactor operators ranged from 1.0 to 7.4 ppm in 1950, and TWA concentrations were 2.9 ppm (range = 0.4-38 ppm) during 1971 and 1972 and 5.0 ppm (range = 1.9-96 ppm) in 1975. Concentrations for still operators ranged from 2.2 to 24 ppm or up to 31 ppm on warm days in 1950 and 1952 and mean TWA concentrations ranged from 3.5 to 4.0 ppm (range = 0-110 ppm) in 1971, 1972, and 1975. Concentrations of 1,2-dibromoethane ranged up to 13.4 ppm when the drums were being filled and up to 71 ppm after a spill. Mean serum bromide concentrations measured from 1957 to 1970 ranged from 2.0 ± 0.8 to 8.7 ± 3.8 mg/dL (overall mean of 5.8 ± 4.5 mg/dL) for reactor operators and 2.0 ± 0.0 to 13.0 ± 0.00 mg/dL (overall mean = 7.4 ± 4.4 mg/dL) for still operators. Background bromine concentrations are #5.0 mg/dL.

The expected numbers of deaths were based on mortality rate of U.S. white males. There were 21deaths (19.5 expected) from all causes at Plant No. 1and 15 deaths (13.0 expected) at Plant No. 2. The number of observed deaths due to specific causes at Plant No. 1 were similar to the number expected. However, at Plant No. 2, five deaths (2.2 expected, $p<0.072$) were caused by neoplasms; two deaths (0.7 expected, N.S.) were due to neoplasms of the digestive system, three deaths (0.9 expected, $p<0.063$) were due to other neoplasms, and two deaths (0.3 expected, $p<0.037$) were due to influenza and pneumonia. No statistically significant correlation was found between the duration of exposure (employment) and increase in the number of deaths. The workers in this cohort were exposed to other chemicals in addition to 1,2-dibromoethane. This study showed no strong correlation between exposure to 1,2-dibromoethane and mortality.

2.3. Developmental/Reproductive Toxicity

A study by Wong et al. (1979b) did not show a statistically significant effect on fertility of male workers at four chemical plants (Plants A, B, C and D) where exposure to

1,2-dibromoethane ranged from <0.05 ppm to 5 ppm (TWA) but did show statistically significant decrease in fertility at one plant. This cohort consisted of 297 married couples in which the men were exposed to 1,2-dibromoethane on the job and fertility was measured indirectly by the number of live births among the wives. Fertility of the wives was compared with the national rate to calculate observed/expected ratios (standardized birth ratio, SBR) adjusted for age, parity, race, and calendar year. A total of 1092 person-years were observed among the 297 couples with an average age of 30-34 years. The number of observed births among exposed workers at Plants A, B, or C was not different from the expected number; however, the observed number of births for workers at Plant D was significantly lower (SBR = 0.50) for exposed white workers and all exposed workers (0.51) and was lower but not significantly for exposed non-white workers. The number of observed births for all four plants combined was not significantly different from the expected number. According to the investigators the statistical power of this study was adequate for detecting a 20% decrease in fertility. Several limitations were noted for this study. Female reproductive performance was used as a measure of fertility in male workers. Except for surgical sterilization, data on contraceptive practices were not obtained from the wives of 1,2-dibromoethane-exposed workers. Person-years were collected for the period immediately following a birth, miscarriages were not counted. National birth data were used for comparison where regional differences in attitudes and behaviors toward child birth and family size may differ. This study was also reported by NIOSH (1977b).

Schrader et al. (1988) described a short-term longitudinal reproductive study on ten male forestry workers (20-32 years of age, average age = 25.1 years) exposed to 1,2-dibromoethane for approximately 6 weeks. Semen quality was measured as sperm count, viability, velocity, and motility, semen volume, and semen pH. Semen samples were collected from the workers 1 to 2 weeks before employment and from a control population consisting of six forestry workers (20-35 years of age, average age = 26.5 years) who had no known exposure to 1,2-dibromoethane. Air samples were collected in the breathing zone of the workers for 15 minutes to 1 hour or for a full 8-hour shift. The concentration of 1,2-dibromoethane in the breathing zone of the forestry workers ranged from not detectable (ND) to 2165 ppb when filling tank trucks, 57 to 525 ppb when spraying logs, and 8-184 ppb when pouring 1,2-dibromoethane over logs. Dermal exposure of these workers was extensive but not quantitated. Semen volume was decreased in 9/10 workers and sperm velocity was decreased in the 10 workers exposed to1,2-dibromoethane compared with 2/6 control workers. Sperm viability, sperm count, and semen pH were similar in 1,2-dibromoethane-exposed and control workers.

In a cross-sectional study, semen parameters were measured in 46 workers exposed to 1,2-dibromoethane when fumigating papaya for fruit flies and compared with 43 unexposed workers from a nearby sugar processing plant, who were of similar age, ethnicity, and socioeconomic background (Ratcliffe et al. 1987, Schrader et al. 1987, 1988). The average duration of employment was 5 years and the geometric mean of the TWA concentrations was 88 ppb (range = 16-175 ppb) with peak exposures ranging from 12 to 262 ppb. The average age was 28.9 years for the exposed workers and 34.4 years for the unexposed workers. The proportion of workers who were current or past cigarette smokers, consumed alcohol or caffeine, or took prescription medication was similar between the two groups, but twice as many 1,2-dibromoethane-exposed workers were marijuana users. Other potential confounders included history of urogenital disorders, history of fever, duration of abstinence, and age of sample before analysis. Parameters evaluated included sperm concentration (per mL), count (per

ejaculate), velocity, motility, morphology, morphometry (area, length, and width of sperm heads), and viability and semen volume and pH.

Statistical adjustments were made for subject's age, but not for other confounding variables, in almost all analyses. Analysis of sperm parameters showed that the average semen volume was not significantly different between the two groups, but the pH was slightly more alkaline in 1,2-dibromoethane-exposed workers than in unexposed workers; the pH difference may have been caused by the age of the samples. Sperm concentration was not significantly different between the two groups of workers; however, the number of sperm per ejaculate was significantly reduced and the percentage of workers with sperm concentrations #20 million/mL was significantly greater in 1,2-dibromoethane-exposed workers (21.7% vs 4.7% for unexposed workers). Sperm viability and motility, after adjusting for worker's age, were significantly decreased among exposed workers, but sperm velocity was not affected. Overall percentage of normal sperm was not affected by exposure to 1,2-dibromoethane, but the proportion of all abnormal sperm and sperm with abnormal tails, tapered heads, or absent heads were significantly increased in exposed workers. Overall, morphometric parameters were similar in exposed and unexposed workers, but the width of the sperm head was significantly reduced in exposed workers. Therefore, this study shows some effects on reproductive parameters in males.

2.4. Genotoxicity

Steenland et al. (1985) found no differences in the frequencies of sister chromatid exchange (SCE) and chromosome aberrations in peripheral lymphocytes from 14 sprayers who used a 1,2-dibromoethane-containing insecticide for control of pine beetles on felled pine trees. Lymphocytes collected from workers before and after a short-term exposure to 1,2-dibromoethane were compared with those from six unexposed controls. Potential confounders included smoking and use of prescription medicines. The workers were 20-32 years old and two were females. They were exposed to 60 ppb (average 8-hour TWA) with a range of 5-281 ppb and a peak range of 8-2165 ppb for 5-26 days as determined by samples collected in the breathing zone of the workers.

Steenland et al. (1986) also analyzed the SCE and chromosome aberrations in peripheral lymphocytes from papaya workers exposed to 1,2-dibromoethane and workers at a sugar mill who were not exposed to 1,2-dibromoethane. The average duration of exposure was 5 years, and the geometric mean of the 8-hour TWA was 88 ppb with peaks up to 262 ppb. No differences in the frequency of SCEs or chromosome aberrations attributed to exposure to 1,2-dibromoethane were observed in exposed workers.

2.5. Summary

Humans exposed to lethal concentrations of 1,2-dibromoethane experienced irritation to the eyes, throat, and respiratory tract; diarrhea and vomiting; and central nervous system effects including restlessness, nervousness, combativeness, and lethargy. Hepatomegaly; and clinical pathologic findings indicative of degenerative changes in the kidney and liver were confirmed histopathologically. Autopsy findings after a lethal exposure include pulmonary edema and congestion of the viscera and brain. Exposure to lethal concentrations of 1,2-dibromoethane also raises the blood bromine level to over 100 times the background level (Letz et al. 1984, Marmetschke 1910). Exposure to nonlethal concentrations of 1,2-dibromoethane causes

swelling of the eyelids, and salivary glands, conjunctival irritation, and respiratory tract irritation, in addition to gastrointestinal discomfort and vomiting (Kochmann 1928).

Epidemiologic studies did not show exposure-related increases in mortality due to neoplastic or non-neoplastic diseases in workers exposed to 1,2-dibromoethane. However, reproductive studies showed decreased sperm velocity and semen volume in workers after short-term exposure (Schrader et al. 1988) and decreased number of sperm/ejaculate, increased percentage of workers with low sperm count, decreased sperm viability and motility, and increased proportion of abnormal sperm after long-term exposure to 1,2-dibromoethane (Ratcliffe et al. 1987, Schrader et al. 1987, 1988). A study on fertility as measured by standardized birth rate in wives of workers exposed to 1,2-dibromoethane did not detect an effect attributed to 1,2-dibromoethane exposure. SCEs and chromosome aberrations in peripheral lymphocytes were not increased in workers after short- or long-term exposures to 1,2-dibromoethane (Steenland et al. 1985, 1986).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Dogs

One dog each was exposed for 1 hour to 1, 2, or 5 mL of 1,2-dibromoethane vaporized in a 100-L glass bell jar (Merzbach 1929). The dogs exposed to 2 or 5 mL of vaporized 1,2-dibromoethane died within 12-18 hours and the one exposed to 1 mL died 3 weeks after exposure. Restlessness and strong salivation were observed 20 minutes after initiating exposure to 5 mL of vaporized 1,2-dibromoethane followed by increased respiration, laying down on its side, and clonic twitching after 25 minutes. The twitching stopped and respiration rate decreased after 45 minutes. Immediately after exposure ended, the dog vomited, trembled severely, had audible rales and rattling in the chest, and could not stand up. The dog lost consciousness 35 minutes after exposure ended and died during the night. Autopsy revealed blood in the lungs; systolic heart; hemorrhaging in the subendocardium, the mucous lining of the intestines and rectum, and the surface of the dura mater; liver congestion; and cloudy cornea. The dog exposed to 2 mL of vaporized 1,2-dibromoethane showed similar but less severe signs of toxicity and died during the night. The dog exposed to 1 mL of vaporized 1,2-dibromoethane showed signs of restlessness, eye irritation, labored respiration, and increased respiration rate during exposure. Milky-blue corneal opacity progressing to purulent conjunctivitis and corneal ulceration was observed 5 hours after exposure ended. Pronounced weight loss and cessation of eating occurred before the dog died 3 weeks after exposure. Autopsy revealed bronchopneumonic foci and severe hyperemia in the lungs, a spherical thrombus in the heart, and fatty degeneration in the liver.

3.1.2. Rats

3.1.2.1. Single Lethal Exposures

Groups of male and/or female rats (strain not specified) were exposed to 1,2-dibromoethane vapor (~100% pure) at concentrations of 10,000, 5000, 3000, 1000, 800, 400, 200, or 100 ppm for durations ranging from 0.02 hours (1.2 minutes) to 16 hours (Rowe et al. 1952). Each group consisted of 4 to 30 rats. Vapor concentrations were determined by combustion analysis for concentrations below 5000 ppm; because of technical difficulties, nominal concentrations were used for 5000 and 10,000 ppm. Analytical concentrations were within ±10% of nominal concentrations. The rats were observed for changes in behavior, body

weight gain, and time of death; surviving animals were observed 2-3 weeks or until recovery appeared to be complete or almost complete. The investigators showed graphically the concentration vs time relationships for $LC_{99.99}$ values (essentially all rats in a group died), LC_{50} values 50% of rats in a group died), and LC_{01} (essentially no rats died).

Mortality data reported by Rowe et al. (1952) are presented in Table 2. The LCt_{99}, LCt_{50}, and LCt_{01} values presented in Table 2 were calculated by NIOSH (1977a). Central nervous system depression was observed in rats exposed to the higher concentrations (not otherwise specified but assumed to be 3000-10,000 ppm). Deaths in groups with $50% mortality occurred within 24 hours and were caused by cardiac and respiratory failure; deaths in groups with <50% mortality occurred up to 12 days after exposure and were caused by pneumonia secondary to pulmonary damage. Clinical signs observed before death included weight loss, rough and unkempt appearance, irritability, and bloody discharge from the nose. Similar symptoms were observed in the survivors before recovery became apparent. Gross findings in rats exposed to concentrations in the lethal range included increased weight of the lungs, liver, and kidneys and microscopic findings included pulmonary congestion, edema, hemorrhage, and inflammation; cloudy swelling, centrilobular fatty degeneration, and necrosis in the liver; and slight interstitial congestion and edema and cloudy swelling in the tubular epithelium of the kidneys. Exposure concentrations and durations estimated to be associated with adverse effects are as follows: 800 ppm for 9 minutes, 200 ppm for 1 hour, and 100 ppm for 4 hours. The adverse effects associated with these concentrations and durations of exposure are increased liver weight and slight histopathologic changes in the liver. The investigators noted that these effects were the most sensitive endpoint and served as the basis for estimating the exposure concentration and durations unlikely to be associated with adverse effects. These are as follows: 800 ppm for 6 minutes, 200 ppm for 42 minutes, 100 ppm for 2.5 hours, or 50 ppm for 7 hours.

TABLE 2. Acute Exposure of Rats And Guinea Pigs to 1,2 Dibromoethane

Concentration (ppm)	Duration of exposure	Mortality	% lethality	Lethal times[a] (LCt)
Rats				
10,000	6.0 min	20/20	100	LCt99.99 = 9 min
	4.2 min	7/10	70	LCt50 = 2.4 min
	3.0 min	2/4	50	LCt01 = 0.6 min
	1.8 min	1/20	5	
	1.2 min	0/20	0	
5000	8.4 min	20/20	100	LCt99.99 = 21 min
	6.0 min	9/10	90	LCt50 = 5.4 min
	4.2 min	5/15	33	LCt01 = 1.8 min
	3.0 min	3/30	10	
	2.4 min	0/20	0	
3000	12 min	5/10	50	LCt99.99 = 36 min
	6 min	0/20	0	LCt50 = 10.8 min
				LCt01 = 3.6 min
1600	30 min	20/20	100	LCt99.99 = 66 min
	24 min	12/15	80	LCt50 = 18 min
	18min	4/15	27	LCt01 = 6 min
	12 min	0/30	0	
800	48 min	13/20	65	LCt99.99 = 132 min
	32.8 min	10/20	50	LCt50 = 45 min
	30 min	4/20	20	LCt01 = 16.8 min
	24 min	4/20	20	
400	5.0 h	20/20	200	LCt99.99 = 7.50 h
	3.0 h	17/20	85	LCt50 = 2.00 h
	2.5 h	19/20	95	LCt01 = 0.62 h
	2.0 h	16/25	64	
	1.4 h	5/25	25	
	1.0 h	2/20	10	
	48 min	1/20	5	
	36 min	0/20	0	
200	16.0 h	19/20	95	LCt99.99 = 42 h
	12.0 h	10/20	50	LCt50 = 12 h
	8.5 h	9/20	45	LCt01 = 2 h
	7.0 h	4/11	36	
	5.0 h	3/10	33	
	4.0 h	0/5	0	
	3.0 h	1/11	9	
	2.0 h	0/5	0	
	1.4 h	0/20	0	
100	16.0	0/20	0	not applicable
	12.0	0/20	0	
	8.5 h	0/20	0	
Guinea pigs				
400	7.0 h	20/20	100	not calculated
	5.0 h	18/20	90	
	3.0 h	5/10	50	
	2.0 h	0/20	0	
200	7 h	0/15	0	not calculated

Source: Rowe et al., 1952

[a]LCt values calculated by NIOSH 1977a.

1
2

3.1.2.2. Repeated Lethal Exposures

Groups of rats (strain not specified) were exposed repeatedly to 1,2-dibromoethane vapor 7 hours/day for various periods of time (Rowe et al. 1952). Ten female rats received up to 7 exposures to 100 ppm in 9 days, 20 male and 20 female rats received 63 exposures to 50 ppm in 91 days (13 weeks), 18 females received 12 exposures to 50 ppm in 16 days, 20 male and 20 female rats received 151 exposures to 25 ppm in 213 days (~30 weeks) and additional groups of 8 and 15 females received 13 exposures in 17 days. Two control groups were included, one unexposed and the other air exposed under conditions similar to that of 1,2-dibromoethane-exposed rats. The rats were weighed twice weekly, observed frequently for clinical signs, and blood was collected periodically for hematologic changes. All rats were necropsied, and the lungs, heart, liver, kidneys, spleen, and testes were weighed and processed for microscopic examination. The pancreas and adrenal glands were examined microscopically.

One rat each died after one, five, and seven exposures to 100 ppm. Survivors of seven exposures were thin and unkempt, had bloody contents in their stomachs, and had increased liver, lung, and kidney weights. Microscopic examination showed thickening of the alveolar wall and leukocytic infiltration in the lungs, extensive cloudy swelling of the liver, and slight congestion and hemosiderosis in the spleen. Since none of the 60 rats exposed one time to 100 ppm for 8.5, 12, or 16 hours died, it is unlikely the one death after exposure to 100 ppm for 7 hours was due to exposure to 1,2-dibromoethane. After repeated exposure to 50 ppm, 50% of the male rats died because of secondary pneumonia and upper respiratory tract infection, whereas only 25% of the females died. Growth was slightly retarded and liver, lung, and kidney weights were increased in both sexes. The testes weight was decreased in males, and the only microscopic finding was evidence of old pneumonic consolidations in the lungs of male rats. Females exposed to 50 ppm had increased liver and kidney weights but no evidence of microscopic damage. After repeated exposure to 25 ppm, 50% of male rats died because of secondary pneumonia and upper respiratory tract infection, but only 15% of females died. No significant organ weight changes or microscopic lesions were observed in rats exposed to 25 ppm. The additional female rats receiving 13 exposures to 25 ppm 1,2-dibromoethane vapor also showed no evidence of adverse effects caused by exposure to 1,2-dibromoethane (Rowe et al. 1952). The secondary pneumonia may not have been due to 1,2-dibromoethane exposure.

3.1.3. Guinea Pigs

Groups of three guinea pigs were exposed to 1,2-dibromoethane at concentrations of 8000, 4000, or 2000 ppm (61,600, 30,800, or 15,400 mg/m^3) for 30, 60, or 150 minutes, respectively (Thomas and Yant 1927). All guinea pigs died within 18 hours after exposure. Signs of nasal irritation and generalized weakness were observed during exposure. Gross and microscopic examinations revealed pronounced granular degeneration of parenchyma tissue of the kidney; less damage in the pancreas, spleen, heart, liver, and adrenals; and swelling and generalized interstitial endemous degeneration of the endothelial lining of the abdominal vascular system (not otherwise described).

Groups of 20 guinea pigs were exposed to 1,2-dibromoethane vapor at 400 ppm for 7.0, 5.0, or 2.0 hr, 10 guinea pigs were exposed to 400 ppm for 3.0 hours, and 15 guinea pigs were exposed to 200 ppm for 7.0 hours (Rowe et al., 1952). The protocol was the same as described for rats. Mortality data are summarized in Table 2. No details were presented on clinical signs or pathologic lesions in the guinea pig exposed to any concentration or duration. One-half to

100% of all guinea pigs exposed to 400 ppm for 3, 5, or 7 hours died during the observation period. No guinea pigs died after exposure to 400 ppm for 2 hours or 200 ppm for 7 hours .

3.1.4. Rabbits

Lucas (1928) exposed two rabbits to 1,2-dibromoethane for about 10 minutes at concentrations sufficient to induce light anesthesia. Signs of irritation (vocalization by the animals) and extremely rapid respiration were observed during exposure. After recovery from anesthesia, the mucous membranes of the mouth were an "old rose" color, probably caused by vascular congestion and cyanosis. The rabbits died within 18 hours. Necropsy showed an enlarged and mottled liver, and microscopic examination showed slight to moderate diffuse fatty changes and marked fatty changes in the portal region of the liver. Another rabbit was exposed to 1,2-dibromoethane for 12 minutes at an unspecified concentrations that produced deep anesthesia. Signs of irritation were similar but more severe than those observed after light anesthesia. Respiratory snuffling was observed after recovery from anesthesia. This animal died within 15 hours and necropsy showed enlarged lungs filled with a frothy exudate and swollen and markedly congested liver. The investigator noted that hydrogen bromide formed from decomposition of 1,2-dibromoethane may have caused the observed effects.

Four female rabbits were exposed to 100 ppm 1,2-dibromoethane vapor, 7 hours/day for 4 days (Rowe et al. 1952). Two rabbits died after the second exposure, one died during the third exposure, and the fourth rabbit was killed after the fourth exposure. The livers of these rabbits showed extensive fatty degeneration and areas of necrosis.

3.2. Nonlethal Toxicity

Nonlethal toxicity of inhaled 1,2-dibromoethane vapor is summarized in Table 3.

3.2.1. Nonhuman Primates

Two monkeys (one male and one female) were exposed 7 hours/day to 50 ppm of 1,2-dibromoethane vapor for 49 exposures in 70 days (10 weeks) or to 25 ppm for 156 exposures in 220 days (~31 weeks) (Rowe et al., 1952). The monkeys exposed repeatedly to 50 ppm lost 5% of their weight and appeared ill, nervous, and unkempt throughout the study. Liver and kidney weights were increased at the end of the study. Slight central fatty degeneration was observed in the liver, but no other significant histopathologic changes were observed in other organs. No adverse effects were observed in the monkeys repeatedly exposed to 25 ppm.

3.2.2. Rats

3.2.2.1. Single nonlethal exposures

None of the rats exposed to 100 ppm of 1,2-dibromoethane for 8.5, 12, or 16 hours died during the 3-week observation period (Rowe et al., 1952). These results are discussed in Section 3.1.2.1. Along with the series of acute lethality exposures to rats, Rowe et al. (1952) estimated concentrations associated with adverse effects and concentrations associated with no adverse effects. These results are discussed in Section 3.1.2.1.

3.2.2.2. Repeated nonlethal exposures

Groups of five male and five female F344 rats were exposed to 1,2-dibromoethane vapor at concentrations of 0, 3, 15, or 75 ppm, 6 hours/day, 5 days/week, for 13 weeks in a dynamic 100-L plexiglass chamber (Reznik et al., 1980). These investigators described only those lesions observed in the nasal cavity. The lesions observed in rats exposed to 15 ppm consisted of cytomegaly, focal hyperplasia, squamous metaplasia, and loss of cilia in one or two male or female rats. Four or five male and female rats exposed to 75 ppm had similar lesions in the nasal cavity.

Groups of 4-5 male and 5-6 female F344 rats were exposed to 1,2-dibromoethane vapor at concentrations of 0, 3, 15, or 75 ppm, 6 hour/day, 5 days/week for 90 days (NTP 1982). Exposure conditions are assumed to be similar to those described for the carcinogenicity study (Section 3.6). Clinical signs were not reported after one or two exposures. Male rats exposed to 3 ppm gained 8% less weight than controls, and males exposed to 15 and 75 ppm gained 27% and 42% less weight, respectively, than controls, whereas females exposed to 3 and 15 ppm gained 30% and 16% more weight, respectively, than controls and females exposed to 75 ppm gained 36% less weight than controls. No rats died during the study. Microscopic examination showed increased incidences of swelling and/or vacuolation of the zona fasciculata in the adrenal cortex and a slight decrease in follicular size in the thyroid gland at 75 ppm in both sexes. No liver or kidney lesions were observed in male or female rats exposed to any concentration.

Nitschke et al. (1980, 1981) reported on a study in which groups of 40 male and 20 female F344 rats were exposed to 1,2-dibromoethane vapor at 0, 3, 10, or 40 ppm, 6 hours/day, 5 day/week in a dynamic stainless steel and glass Rochester-type chamber. Ten males per group were sacrificed after 1 week (5 exposures), 6 weeks (29 exposures), 13 weeks (67 exposures), and 88-89 days post-exposure (recovery). Ten females per group were sacrificed after 13 weeks and after the recovery period. Chamber atmospheres were analyzed three times each day by gas chromatography using flame ionization detection. No exposure-related effects were observed at 3 ppm. Males exposed to 40-ppm showed signs of eye and nasal irritation during the "first exposure period" (no other information was provided) but not those exposed for longer exposure or to other concentrations. Relative liver weight was slightly elevated in males exposed to 40 ppm for 6 or 13 weeks. Relative liver weight was elevated in females exposed to 10 ppm, and absolute and relative liver weights were elevated in females exposed to 40 ppm. The only microscopic lesion in the liver was slight fatty vacuolation in two females exposed to 40 ppm. The most sensitive target in this study was the nasal turbinates, where microscopic lesions were found primarily in the anterior region (respiratory epithelium). These lesions consisted of very slight to slight hyperplasia of the respiratory epithelium in male rats exposed to 10 ppm for 1, 6, or 13 weeks and females exposed to 10 ppm for 13 weeks and very slight to slight epithelial cell necrosis in one male rat exposed for 13 weeks. Very slight single epithelial cell necrosis was observed in one male rat exposed to 10 ppm for 1 or 13 weeks but not for 6 weeks. Similar hyperplastic lesions in the respiratory epithelium were observed in male rats exposed to 40 ppm for 1 or 6 weeks, but the lesions progressed to very slight to slight nonkeratinizing squamous metaplasia and hyperplasia in all males and females exposed to 40 ppm for 13 weeks. In addition, very slight individual epithelial cell necrosis was observed in the respiratory epithelium in males and females exposed to 40 ppm for 13 weeks. The lesions resolved in all rats during the recovery period except for one female that had isolated focal epithelial hyperplasia in the respiratory epithelium.

3.2.3. Mice

Groups of ten male and ten female B6C3F$_1$ mice were exposed to 1,2-dibromoethane vapor at concentrations of 0, 3, 15, or 75 ppm, 6 hours/day, 5 days/week, for 13 weeks in a dynamic 100-L plexiglass chamber (Reznik et al., 1980). This report focused only on nasal cavity lesions. Two or three of ten male mice and eight or nine of ten female mice exposed to 75 ppm had nasal cavity lesions consisting of cytomegaly, focal hyperplasia, squamous metaplasia, and loss of cilia. None of the mice in the control, 3- or 15-ppm groups had lesions in the nasal cavity.

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 1,2-dibromoethane (>99% purity) vapor at 0, 3, 15, or 75 ppm, 6 hours/day, 5 days/week, for 90 days (NTP 1982). Exposure conditions are assumed to have been similar to those described for the carcinogenicity study (Section 3.6). Six male mice exposed to 3 ppm died and one female exposed to 75 ppm died during the study. No other effects in the mice were associated with lethality; therefore, it is unlikely that the deaths were related to exposure to 1,2-dibromoethane. Clinical signs were not reported following one or two exposures. Weight gain by males at 3 ppm was similar to that of controls but was 21% and 36% less than that of controls at 15 and 75 ppm, respectively. Females exposed to 3 and 15 ppm gained 15% less weight than controls and females exposed to 75 ppm gained 25% less weight than controls. Eye irritation was observed near the end of the study and megalocytic cells were found in the bronchioles of three males and nine females exposed to 75 ppm, but not after a single exposure.

3.2.4. Guinea pigs

None of the 15 guinea pigs exposed to 1,2-dibromoethane vapor at 200 ppm for 7 hours as described in Section 3.1.3 died during the 2-3 week observation period (Rowe et al. 1952) . Clinical signs and pathologic lesions were not described.

All eight male and eight female guinea pigs exposed to 50 ppm of 1,2-dibromoethane, 7 hours/day for 57 days in an 80-day period survived, but growth was significantly depressed throughout the study (Rowe et al. 1952). Lung, liver, and kidney weights were increased. Slight central fatty degeneration was observed in the liver, and slight interstitial congestion and edema and slight parenchyma degeneration in the tubular epithelium were observed in the kidney. The lungs, heart, spleen, adrenals, pancreas, and testes were not affected. Rowe et al. (1952) reported no adverse effects in a group of eight female guinea pigs exposed to 25 ppm of 1,2-dibromoethane, 7 hours/day for 13 days within a 17-day period or in groups of eight male and eight female guinea pigs similarly exposed for 145 times in a 205-days period (~29 weeks). Although four males and two females exposed 145 days died of pulmonary infection, the investigators did not attribute the deaths to 1,2-dibromoethane exposure.

3.2.5. Rabbits

Two female rabbits exposed to 100 ppm of 1,2-dibromoethane, 7 hours/day for 2 days lost weight and had a slight cloudy swelling in the liver. One female and three male rabbits exposed 59 times to 50 ppm in 84 days (12 weeks) or 152 times to 25 ppm in 214 days (~31 weeks), 7 hours/day had a slight increase in liver and kidney weights but no other effects attributed to exposure to 1,2-dibromoethane (Rowe et al. 1952).

TABLE 3. Summary of Nonlethal Effects of Inhaled 1,2 Dibromoethane Vapor in Experimental Animals

Species/Strain/Sex	Expt. Protocol	Effects/Comments	Reference
Rats/	100 ppm, 8.5, 12.0, & 16.0 h	No lethality	Rowe et al. 1952
Rat/F344/M&F	0, 3, 15, 75 ppm, 6 h/d, 5 d/wk, 13 wks	Systemic: dec. wt. gain 15 (M) & 75 ppm (M/F; adrenal cortical and thyroid follicular lesions (F); Nasal cavity: no effect at 3 ppm lesions (cytomegaly, hyperplasia, metaplasia, cilia loss) at 15 & 75 ppm	NTP 1982; Reznik et al. 1980
Rat/F344/M&F	0, 3, 10, 40 ppm, 6 h/d, 5 d/wk, 13 wks	Systemic: mild liver lesions at 40 ppm Nasal cavity: hyperplasia & single cell necrosis at 10 ppm and also squamous metaplasia at 40 ppm; no effect at 3 ppm	Nitschke et al. 1980, 1981
Mice/B6C3F1/M&F	0, 3, 15, 75 ppm, 6 h/d, 5 d/wk, 13 wks	Systemic: dec. wt. gain 3 (F), 15 & 75 ppm (M&F) Nasal cavity: no effect at 3 or 15 ppm; lesions (cytomegaly, hyperplasia, squamous metaplasia, cilia loss) at 75 ppm; other effects: eye irritation and megalocytes in bronchioles at 75 ppm	NTP 1982; Reznik, 1980
Guinea pigs/M&F	200 ppm for 7 h	No effects observed	Rowe et al., 1952
Guinea pigs/M&F	50 ppm, 7 h/d. 57 exposures in 80 d	Growth depression, increase in liver, lung, kidney wt., microscopic lesions in liver & kidney	Rowe et al 1952
Guinea pigs/M&F	25 ppm, 7 h/d, 13 exposures in 17 d & 145 exposures in 205 d	No effects observed	Rowe et al. 1952
Rabbits/F	100 ppm, 7 h/d, 2 d; 50 ppm, 7 h/d, 59 exposures in 84 d; 25 ppm, 7 h/d, 152 exposures in 214 d	Weight loss & microscopic lesion in liver at 100 ppm slight increase in liver wt at 50 ppm	Rowe et al. 1952
Monkeys/M&F	50 ppm, 7 h/d, 49 exposures in 70 d 25 ppm, 7 h/d, 156 exposures in 220 d	Weight loss, increase in liver and kidney wt., microscopic lesions in liver	Rowe et al 1952

3.3. Neurotoxicity

In a developmental neurotoxicity study, Smith and Goldman (1983) exposed groups of pregnant female Long-Evans rats to 1,2-dibromoethane vapor at concentrations of 0, 0.43, 6.67, or 66.67 ppm 4 hours/day, 3 days/week from gestation day (GD) 3-20 and studied the behavior of the dam and offspring. The exposure concentrations were monitored and maintained by flow meter settings and periodic re-calibration of the flow meter. Maternal behavior was evaluated for nest building and pup retrieval. The offspring were subjected to a battery of neurotoxicity tests consisting of the rotorod, open field activity, passive avoidance, runaway latency, DRL-20, and T-maze discrimination. Defecation was increased in a dose-related manner during exposure of dams and body weight was increased by only 49.6% in the 66.67-ppm group compared with a 63% increase in the control group. No effect was observed on maternal nest building or pup retrieval. Body weight of pups at 66.67 ppm was less than that of controls, but the difference was resolved in adulthood. The neurotoxicity tests showed no differences between treated and control groups except for the rotorod and T-maize tests. Offspring in the 6.67- and 66.67-ppm

groups performed significantly better than controls at 30 and 63 days of age and had a greater number of correct responses and reduced latency to correct response than the controls. Therefore, this study did not show evidence of developmental neurotoxicity in the offspring because the exposed group performed as well as or better than the controls.

Pregnant rats were exposed to 1,2-dibromoethane vapor at 0.5 mg/L (65 ppm) for 6 hours or 1 mg/L (130 ppm) for 3 hours on GD 10, 11, and 12 and offspring were observed up to 4 weeks after weaning (Vodickova et al., 2003). The strain, number of dams exposed, and the number of live offspring produced or tested was not reported. Transient maternal toxicity (not otherwise described), increased numbers of dead fetuses, and a higher level of spontaneous activity in offspring were observed at 130 ppm. Offspring in the 65-ppm group showed reduced exploratory activity, reduced peak night activity, and lower index of neurobehavioral development (11^{th} day of testing). The investigators concluded that exposure to 1,2-dibromoethane affected behavior of the offspring until they were at least 8 weeks of age. No other details were available. This study was cited from an abstract; a full report will not be made available. Due to the limited information available in this abstract, the data from this study were not used.

3.4. Developmental/Reproductive Toxicity

3.4.1. Rats

Groups of 15-17 pregnant Charles River CD rats were exposed to 1,2-dibromoethane (99%) at concentrations of 20, 38, or 80 ppm, 23 hours/day during GD 6-15 and sacrificed on GD 20 for evaluation of fetal development (Short et al. 1977, 1978). Two control groups exposed to room air were included in the study, one was provided food *ad libitum* and another was on a restricted diet. The animals were exposed in 3.5-m^3 Rochester-type stainless steel chambers; chamber atmospheres were monitored by gas chromatography and flame ionization detection. Maternal toxicity was observed at all concentrations, and toxicity was excessive at 80 ppm. Half the dams exposed to 80 ppm died during the study; the surviving dams lost considerable weight and consumed very little food during the exposure period and continued to consume less food and gain less weight than controls after exposure ended. None of the 80-ppm dams produced a live litter; 88% of the implants ended in early resorptions and the remainder as dead fetuses. Dams exposed to 20 and 38 ppm lost weight or gained less weight than controls and consumed less food during the exposure period. No decrease in the number of viable fetuses was observed at 20 or 38 ppm, but fetuses at 38 ppm weighed slightly less than the controls fed. Exposure to 20 and 38 ppm of 1,2-dibromoethane had no effect on soft-tissue or skeletal abnormalities in fetuses, and no exposure-related malformations were observed at any concentration. Early resorptions and fetal deaths precluded evaluation of malformations at 80 ppm.

Short et al. (1979) studied effects of inhaling 1,2-dibromoethane on reproductive parameters in male and female Charles River CD rats. Groups of male rats were exposed to 0, 19, 39, or 89 ppm and groups of female rats were exposed to 0, 20, 38, or 80 ppm 1,2-dibromoethane vapor, 7 hours/day, 5 days/week for 10 or 3 weeks, respectively. Nine or ten males per group were killed at the end of exposure for determination of testicular weight and serum testosterone levels, and the same numbers per group were mated with virgin females (1:2 ratio) once a week for 2 weeks; these males were killed after mating. After exposure, 20 females per group were mated with proven male breeders (2:1) for up to 10 days or until evidence of mating was obtained. Females were not exposed to 1,2-dibromoethane after mating. The

females from both groups were killed mid-gestation for evaluation of numbers of implants, viable implants, and resorptions. The exposed males were examined for histopathologic lesions in the liver, testes, epididymides, prostate, and seminal vesicles and the females were examined for histopathologic lesions in the ovaries and uterus.

Short et al. (1979) reported that 7/33 male rats died after exposure to 89 ppm. None of the males exposed to 89 ppm impregnated even one female rat. Pronounced adverse effects were observed on weight gain, food consumption and serum testosterone level. Moderate to severe atrophy of the testes, epididymis, prostate, and seminal vesicles was observed in all males exposed to 89 ppm. Reduced body weight was observed at termination of exposure of males to 39 ppm and no adverse effects were observed in males exposed to 19 ppm. A total of 10/50 females died after exposure to 80 ppm group and none had normal estrous cycles until 3-4 days postexposure . Only 8/20 females exposed to 80 ppm mated, and all that mated became pregnant. The number of viable implants/dam in females exposed to 80 ppm was reduced by 30% compared with that of controls. No exposure-related histopathological lesions were observed in the ovaries. Because of the marked decrease in food consumption and consequently, weight gain, it is not possible to attribute the effects in male and female rats specifically to 1,2-dibromoethane exposure. There were discrepancies regarding the numbers of male and female rats exposed to 1,2-dibromoethane.

3.4.2. Mice

Groups of 18-22 pregnant CD-1 mice were exposed to 1,2-dibromoethane (99%) vapor at concentrations of 20, 38, or 80 ppm 23 hours/day during gestation days (GD) 6-15 and sacrificed on GD 18 for evaluation of fetal development (Short et al. 1977, 1978). Two control groups exposed to room air were included in the study, one was provided food *ad libitum* and the other was on a restricted diet. The animals were exposed in 3.5-m^3 Rochester-type stainless steel chambers, and chamber atmospheres were monitored by gas chromatography and flame ionization detection. None of the mice exposed to 80 ppm survived and four mice exposed to 38 ppm died during the study. The mice exposed to 38 ppm consumed less food during and after the exposure period, loss weight during exposure, and gained less weight than controls after exposure. Mice exposed to 20 ppm also gained less weight and consumed less food than controls during the exposure period. The number of viable fetuses at 38 ppm was markedly reduced because of increases in early and late resorptions. Fetal body weight also was reduced at 20 ppm. The incidences (based on fetuses per litter) of several soft-tissue anomalies were increased at 38 ppm and the incidences of skeletal anomalies were increased at 20 and 38 ppm. The skeletal anomalies were associated with abnormal ossification, which is indicative of fetal growth retardation.

3.5. Genotoxicity

3.5.1. In vivo studies

The genetic toxicity of 1,2-dibromoethane has not been tested in *in vivo* systems where animals were exposed by inhalation. No effects were observed on SCE, chromosome aberrations, micronuclei formation or cell cycle kinetics in CD1 male mice following i.p. injection of 1,2-dibromoethane in corn oil at doses of 0, 42, 84, or 168 mg/kg (Krishna et al., 1985). According to the review by IARC (1999), 1,2-dibromoethane administered orally or by i.p injection induces DNA strand breaks, cross-links, or related damage in rat and mouse liver cells and in rat testicular germ cells, but does not induce micronuclei in mouse bone-marrow

cells, or dominant lethality in mice or rats. 1,2-Dibromoethane binds covalently to DNA, RNA, and protein in mouse and rat liver, kidney, stomach, and lung cells. 1,2-Dibromoethane also did not induce unscheduled DNA synthesis in mouse hepatocytes *in vivo*; mixed results were produced for rat hepatocytes.

Brittebo et al. (1991) demonstrated by autoradiography that radiolabeled 1,2-dibromoethane injected intravenously into C57BL mice binds irreversibly to the conjunctival epithelium of the eye, cells in the excretory ducts of the intraorbital lacrimal gland and the nasolacrimal duct. Radioactivity was not found above background in the skin, connective tissue, or sebaceous glands of the eyelid.

3.5.2. In vitro studies

1,2-Dibromoethane is mutagenic in *Salmonella typhimurium* strains TA 1535 (Rannug et al 1978; Kerklaan et al. 1983) and TA 100 (Kerklaan et al. 1985). Mutagenicity is enhanced in TA1535 by the addition of rat liver S9 fraction (Rannug et al. 1978) and markedly reduced in glutathione deficient (GSH^-) strains of TA1535 and TA100 (Kerklaan et al. 1983, 1985). The mutagenic potential is restored when GSH^- strains are incubated with glutathione. IARC (1999) conducted a comprehensive review on the genotoxicity data of 1,2-dibromoethane and reported that 1,2-dibromoethane is genotoxic in other strains of *Salmonella typhimurium* strains (TA98 and TA1530), *Escherichia coli*, *Streptomyces coelicolor*, *Aspergillus nudulans* with or without metabolic activation, and in *Drosophila melanogaster* (sex-linked recessive lethal mutation and somatic mutation assays). 1,2-Dibromoethane induces DNA strand breaks, cross-links, unscheduled DNA synthesis, gene mutations, chromosomal aberrations, or SCEs in cultured rat testicular germ cells, rat and mouse hepatocytes, Chinese hamster ovary cells, mouse lymphoma L5178Y cells, Chinese hamster lung V79 cells, human epithelial-like cells, human lymphoblastoid cell lines, and human lymphocytes (IARC, 1999). 1,2-Dibromoethane is genotoxic in cultured mammalian cells without exogenous metabolic activation. These reports show that 1,2-dibromoethane is genotoxic in all *in vitro* systems tested.

3.6. Chronic Toxicity/Carcinogenicity

3.6.1. Rats

Groups of 50 male and 50 female F344 rats were exposed to 1,2-dibromoethane vapor at concentrations of 0, 10, or 40 ppm 6 hour/day, 5 days /week for 104 weeks, 103 weeks, or 88-91 weeks, respectively (NTP, 1982). Chamber atmospheres were analyzed 4 times each day by gas chromatography and electron capture detection, and the mean analytical concentrations were 10.02, and 38.93 ppm, respectively. Clinical signs were not reported for rats receiving the first and second exposures. Only 5/50 male rats in the 40-ppm group survived to week 89 compared with 35/50 in the 10-ppm group and 38/50 controls; only 8/50 female rats in the 40-ppm group survived to week 91 compared with 39/50 in the 10-ppm group and 38/50 controls. The incidences of neoplasms in male and female rats are summarized in Table 4. Neoplasms were induced in the nasal cavity and circulatory system of both sexes, tunica vaginalis of males, and lungs and mammary gland of females.

Groups of 48 male and 48 female Sprague-Dawley rats were exposed to 1,2-dibromoethane (99% pure) at concentrations of 0 or 20 ppm, 7 hours/day, 5 days/week for 18 months (Wong et al., 1982). The rats were exposed in 4.5-m^3 stainless steel Rochester-type chambers; the chamber atmosphere was monitored three times a day by gas chromatography.

All rats were observed for clinical signs, morbidity, and mortality, weight gain, hematological changes, and gross and microscopic lesions. Only 7 male and 11 female rats exposed to 1,2-dibromoethane were alive at the end of the study. Body weight was significantly reduced in males 15 months after study initiation and in females at study termination. Food consumption was not significantly reduced, and hematologic parameters were not affected by exposure in either sex. Atrophy and hemosiderosis in the spleen of males were the only non-neoplastic findings observed at significantly increased incidences in exposed rats. Neoplasms were observed in the spleen, adrenal gland, and subcutaneous tissue of males and in the spleen, adrenal glands, and mammary gland of females (Table 4). The total number of tumor-bearing male (25/48) and female rats (29/48) was significantly increased in the groups exposed to 1,2-dibromoethane compared with the controls (8/48 and 7/48, respectively).

3.6.2. Mice

Groups of 50 male and 50 female $B6C3F_1$ mice were exposed to 10 ppm of 1,2-dibromoethane vapor for 103 weeks or 40 ppm for 90 weeks or to filtered air for 104 weeks (Stinson et al., 1981). All animals were exposed 6 hours/day, 5 days/week. Chamber atmosphere was monitored continuously by infrared spectrophotometry. Nasal cavities of all animals were processed for light microscopic examination. Focal hyperplasia was observed in 10/46 males and 11/49 females exposed to 40 ppm and 3/49 females exposed to 10 ppm compared with 0/45 male and 0/50 female controls. Benign neoplasms were observed in both sexes and carcinomas and hemangiosarcoma were observed in females at 40 ppm (Table 4).

Groups of 50 male and 50 female $B6C3F_1$ mice were exposed to 0, 10, or 40 ppm of 1,2-dibromoethane vapor 6 hours/day, 5 days/week for 78-79 weeks for males and 104, 103, and 90 weeks, respectively, for females (NTP 1982). Chamber atmospheres were analyzed 4 times each day by gas chromatography and electron capture detection, and the mean analytical concentrations were 10.02, and 38.93 ppm, respectively. Survival was 13/50, 11/50, and 18/50 in male mice and 40/50, 19/50, and 7/50 in female mice in the 0, 10-, and 40-ppm groups, respectively. The incidences of neoplasms in mice are summarized in Table 4. Neoplasms were found in the lungs of males and the nasal cavity, lower respiratory tract, circulatory system, and mammary glands of females.

Adkins et al. (1986) conducted a lung tumor bioassay in female strain A/J mice exposed to 1,2-dibromoethane (98-99% purity) vapor at concentrations of 0, 20, or 50 ppm, 6 hours/day, 5 day/week for 6 months. Chamber concentrations were monitored by infrared spectrophotometry. The mice were sacrificed at the end of treatment and the number of lung adenomas was counted and a histopathological description of the tumors was provided. Two studies were conducted, one with 30 mice/group (Study 1) and one with 60 mice/group (Study 2). Mortality was observed in both studies, but a larger percentage of animals in Study 1 died compared with Study 2. Exposure to 1,2-dibromoethane resulted in a concentration-related increase in the tumor response. The incidence of lung adenoma, number of tumors/mouse, and number of tumors/tumor-bearing mouse were increased compared with that of the sham-exposed controls (Table 4).

TABLE 4. Inhalation Exposure to 1,2 dibromoethane: Summary of Carcinogenicity Studies

Experimental Animals			Experimental Protocol	Response		Reference
Species/ Strain	Sex	#/Group		Tissue/Tumor Type	Incidence	
Rat/F344	M	50	0, 10, or 40 ppm, 6 h/d, 5 d/wk,104, 103, & 88 wks	Nasal Cavity/multiple types	0/50, 39/50*, 41/50*	NTP, 1982
				Circulatory/hemangiosarcoma	0/50, 1/50, 15/50*	
				Tunica vaginalisis/ mesothelioma (NOS or malig.)	1/50, 8/50*, 25/50*	
Rat/F344	F	50	0, 10, or 40 ppm, 6 h/d, 5d/wk, 104, 103, 91 wks	Nasal Cavity/multiple types	1/50, 34/50*, 43/50*	NTP, 1982
				Lung/alveolar-bronchiolar carcinoma/adenoma	0/50, 0/48, 5/47*	
				Circulatory/hemangiosarcoma	0/50, 0/50, 5/50*	
				Mammary gland/ fibroadenoma	4/51, 29/50*, 24/50*	
Rat/ S-D	M	48	0 or 20 ppm, 7 h/d, 5 d/wk, 18 mo.	Spleen/hemangiosarcoma	0/48, 10/48*	Wong et al., 1982
				Adrenal/ pheochromocytoma, cortical adenoma/carcinoma	2/48, 11/48*	
				Subcutaneous/ mesenchymal tumor	3/48, 11/48*	
Rat/ S-D	F	48	0 or 20 ppm, 7 h/d, 5 d/wk, 18 mo.	Spleen/hemangiosarcoma	0/48, 6/48*	Wong et al., 1982
				Adrenal/ pheochromocytoma, cortical adenoma/carcinoma	1/48, 6/48*	
				Mammary/ adenoma, fibroadenoma, carcinoma, adenocarcinoma	2/48, 25/48*	
Mouse/ B6C3F1	M	50	0, 10, or 40 ppm, 6 h/d, 78-79 wks	Lung/alveolar/bronchiolar adenoma/carcinoma	0/41, 3/48, 23/46*	NTP, 1982
Mouse/ B6C3F1	F		0, 10, or 40 ppm, 6 h/d, 104, 103, 90 wks	Nasal cavity/ adenoma/carcinoma	0/50, 0/50, 8/50	NTP, 1982
				Respiratory tract (bronchus, bronchiole, lungs)/ multiple types	4/49, 11/49*, 42/50*	
				Circulatory/ hemangioma/ hemangiosarcoma	0/50, 12/50*, 27/50*	
				Mammary gland/ adenocarcinoma	2/50, 14/50*, 8/50*	
Mouse/ B6C3F1	M	50	0, 10, or 40 ppm, 6 h/d, 5 d/wk, 104, 103, 90 wks, respectively	Nasal cavity/squamous papilloma	0/45, 0/44, 3-46	Stinson et al. 1981

TABLE 4. Inhalation Exposure to 1,2 dibromoethane: Summary of Carcinogenicity Studies

Experimental Animals			Experimental Protocol	Response		Reference
Species/ Strain	Sex	#/Group		Tissue/Tumor Type	Incidence	
	F	50	0, 10, or 40 ppm, 6 h/d, 5 d/wk, 104, 103, 90 weeks, respectively	Nasal cavity/squamous papilloma, adenoma	0/50, 0/49, 7/49	Stinson et al. 1981
				Nasal cavity/squamous carcinoma, adenocarcinoma, mixed carcinoma	0/50, 0/49, 7/49	
				Nasal cavity/ hemangiosarcoma	0/50, 1/49, 2/49	
Mouse/A/J	F	30	0, 20, or 50 ppm, 6 h/d, 6 months	Lung/adenoma	1.91, 6.51*, 17.0* tumors/tumor-bearing mouse	Adkins et al. 1986
		50	0. 20. or 50 ppm, 6 h/d, 6 months	Lung/adenoma	1.27, 1.87*, 15.3* tumors/tumor-bearing mouse	Adkins et al. 1986

NOS = not otherwise specified
*p#0.05, statistically significant compared with the controls.

3.7. Summary

In acute inhalation studies, the LC_{50} values for rats exposed to 1,2-dibromoethane were 10,000 ppm for 2.4 min, 5000 ppm for 5.4 min, 3000 ppm for 10.8 min, 1600 for 18 min, 800 ppm for 45 min, 400 ppm for 2 hours, and 200 ppm for 12 hours. The lowest lethal concentration for rats was 200 ppm for 3 hours and 400 ppm for 48 minutes. Guinea pigs died after single exposures to 400, 2000, 4000, and 8000 ppm for 180,150, 60, and 30 minutes, respectively. Rabbits died after two, 7-hour exposures to 100 ppm. Respiratory tract irritation and microscopic lesions in the lungs, liver and kidney are the primary pathologic effects after exposure to lethal concentrations; however, deaths were attributed to cardiac and respiratory failure or to secondary pneumonia resulting from pulmonary damage when death was delayed. Other organs affected by inhalation exposure to lethal concentrations of 1,2-dibromoethane vapor include spleen, adrenals, and abdominal vascular system.

A single exposure of rats to 100 ppm for 8.5-16 hours or guinea pigs to 200 ppm for 2 hours caused no deaths or other adverse effects. The non-lethal effects of repeated exposures are summarized in Table 3. In developmental neurotoxicity studies, no effect was observed in rat offspring after exposure of dams to #67 ppm, 4 h/day, 3 days/week on GD 3-20, but evidence of neurotoxicity and abnormal behavior was observed in rat offspring after exposure to 65 ppm, 6 h/day on GD 10-12. No fetuses survived after *in utero* exposure to 135 ppm (3 hr/day). No live fetuses were produced when female rats were exposed to 80 ppm (23 hours/day) during organogenesis and fetal survival was reduced when mice were exposed to 38 ppm under the same conditions. No effect was observed on rat fetuses after exposure to 20 or 38 ppm, but growth retardation was observed in mouse fetuses after exposure to 20 ppm. Daily exposure of male rats to 89 ppm for 10 weeks caused infertility, whereas no effect was observed at 19 or 39 ppm . No reproductive toxicity was observed in females exposed to 80 ppm for 3 weeks.

1,2-dibromoethane is genotoxic after parenteral administration, inducing DNA binding, unscheduled DNA synthesis, DNA strand breaks, cross-links, and other forms of DNA damage in mouse and rat liver or kidney cells and in rat testicular germ cells. Dominant lethality and chromosome aberrations were not observed. Mixed results were observed in studies on the induction of SCEs. 1,2-Dibromoethane binds covalently to DNA in liver, kidney, stomach and lungs. 1,2-Dibromoethane was positive in almost all *in vitro* genetic toxicity tests in *Salmonella typhimurium*, *E. coli*, *Streptomyces*, *Aspergillus*, and *Drosophila melanogaster*. DNA strand breaks and other forms of DNA damage, unscheduled DNA synthesis, SCEs, and chromosome aberrations were induced in cultured human and non-human mammalian cells without metabolic activation. Long-term studies showed that 1,2-dibromoethane is carcinogenic in rats and mice, inducing neoplasms in the nasal cavity and lungs, blood vessels, adrenal gland, and mammary gland of both species, and the tunica vaginalis in rats.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

The metabolism and disposition of 1,2-dibromoethane *in vivo* and *in vitro* has been the subject of detailed reviews by U.S. EPA (2004), IARC (1999), and WHO (1996). Because the database on the metabolism of 1,2-dibromoethane is very large, information from these reviews has been incorporated into the summary presented below.

Watanabe et al. (1978) studied the fate of inhaled 1,2-dibromoethane in male rats (strain not reported) in rats were to 7, 25, or 75 ppm of [C^{14}]-labeled 1,2-dibromoethane for 6 hours. The study authors did not estimate the amount of radioactivity inhaled or systemic uptake. The major route of excretion was urine, which accounted for about 80% of the radioactivity recovered at each exposure concentration. The half-life ($t_{1/2}$) of urinary excretion was 5.1-5.6 hours. The study authors noted that the urinary metabolites were glutathione conjugates and that detoxification is more efficient at 6-7 ppm than at 25 or 75 ppm. This is essentially implying that glutathione conjugation is saturated at the higher exposures.

Wormhoudt et al. (1998) studied the fate and disposition of 1,2-[^{14}C]-dibromoethane in male Wistar rats administered of 50 or 150 mg/kg orally or 10 or 50 mg/kg intravenously and followed the elimination of radioactivity in expired air for up to 8 hours and urine and feces for 168 hours. Urinary excretion accounted for 74.7-82.1% of the dose and fecal excretion accounted for 3.2-4.0% of the dose regardless of dose or route of administration. Expired air accounted for only 0.5-0.8% of the dose administered orally and 6.0-7.2% of the dose administered intravenously. Most of the dose was excreted during the first 48 hours. Organ uptake per gram of tissue was greatest in the liver and red blood cells followed by kidney, lung, and spleen. Three major urinary metabolites were *S*-(2-hydroxyethyl)-mercapturic acid (2-HEMA), thiodiacetic acid (TDA), and thiodiacetic acid sulfoxide (TDA-SO); accounted for almost 80% of the radioactivity recovered in urine. Elimination $t_{1/2}$ for the three metabolites after intravenous administration of 1,2-dibromoethane were 6.3-11.8 hours for 2-HEMA, 4.9-7.0 hours for TDA, 7.8-8.4 hours for TDA-SO), and 6.8-6.9 hours for the sum of TDA and TDA-SO.

1,2-Dibromoethane is metabolized by two pathways: microsomal oxidation (cytochrome P450 pathway) and glutathione conjugation (glutathione-S-transferase pathway), and both pathways produce reactive metabolites. The microsomal oxidative pathway produces the metabolite 2-bromoacetaldehyde (Hill et al., 1978), and the glutathione-S-transferase pathway produces the metabolite 2-HEMA (Nachtomi, 1970). 2-Bromoacetaldehyde can be further

oxidized to bromoethanol and 2-bromoacetic acid followed by conjugation to glutathione via glutathione-S- transferase forming S-(2-hydroxyethyl) glutathione and S-carboxymethylglutathione (Jean and Reed, 1992, U.S. EPA, 2004). Bromoacetaldehyde binds to proteins and is not associated with carcinogenicity but is considered to be responsible to tissue toxicity (IARC, 1999; Ploemen et al., 1997). Bromoacetaldehyde is debrominated during oxidative metabolism and the increased bromine may be important in intitiating lipid peroxidation (Guha et al., 1993; IARC, 1999; U.S. EPA, 2004); glutathione conjugation may also contribute to cytotoxicity (U.S. EPA, 2004). Bromoacetaldehyde also binds to DNA but the reaction is very slow (Guengerich et al., 1981).

Aragno et al. (1996) analyzed malondialdehyde (MDA) as a measure of lipid peroxidation in hepatocytes and serum sorbitol dehydrogenase (SDH) as a measure of hepatocyte toxicity (cytolysis) in rats pretreated with ethanol, methylpyrazole (PYR), or disulfram followed by oral treatment with 1,2-dibromoethane. Ethanol potentiates 1,2-dibromoethane lipid peroxidation and hepatocyte toxicity; PYR inhibits alcohol dehydrogenase activity and prevents the production of aldehyde, and disulfram inhibits aldehyde dehydrogenase activity and causes an increase in aldehyde. 1,2-Dibromoethane treatment caused an increase in SDH, which was markedly potentiated by pretreatment with ethanol. PYR treatment caused a lesser increase in serum SDH than did ethanol. Ethanol also greatly increased lipid peroxidation in 1,2-dibromoethane-treated rats. The investigators showed that ethanol had no effect on cytochrome P450 levels or dimethylnitrosamine demethylase (CYP2E1 isoenzyme) activity, but ethanol inhibited glutathione-S-transferase activity and prevented the depletion of glutathione. These results showed that when glutathione-S-transferase activity is suppressed or inhibited in 1,2-dibromoethane treated rats, bromoacetaldehyde, which is more toxic than the parent compound, accumulates in the cell because it is not further metabolized by conjugation with glutathione. This study demonstrated that toxicity of 1,2-dibromoethane is primarily associated with the oxidative pathway.

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1,2-Dibromoethane undergoes glutathione conjugation to form S-(2-bromoethyl) GSH which spontaneously re-arranges to form thiiranium. Thiiranium is an episulfonium ion (a half mustard) that binds to DNA. Thiiranium may also be hydrolyzed to S-(hydroxyethyl) glutathione and eventually to S-(hydroxyethyl) mercapturic acid, which is excreted is urine (U.S. EPA, 2004). Other urinary metabolites identified in rats administered 1,2-dibromoethane are thiodiacetic acid (TDA) and thiodiacetic acid sulfoxide (TDA-SO); these metabolites are products of the cytochrome-P450 oxidative pathways (U.S. EPA, 2004). Inskeep and Guengerich (1984) showed that the presence of radioactive 1,2-dibromoethane, the glutathione-S-transferase pathway produces a metabolite that binds to DNA; they also demonstrated that the DNA binding did not occur in the presence of microsomal protein with or without NADPH indicating that the glutathione-S-transferase pathway and not the cytochrome P450 pathway produces DNA reactive metabolites. Therefore, it is likely that the glutathione-S-transferase pathway is responsible for genetic toxicity and carcinogenicity.

Cytochrome P450 metabolism is mediated by CYP2E1, 2A6, and 2B6, but the 2E1 isoenzyme is the most active accounting for 97% of the P450 activity catalyzing the metabolism of 1,2-dibromoethane (Ploemen et al., 1997). Cytochrome P450 metabolism showed saturable kinetics, whereas glutathione-S-transferase showed pseudo-first-order kinetics (Ploemen et al., 1997). In rats, the oxidative pathway is predominant over the glutathione conjugative pathway at a ratio of 4:1 (van Bladeren et al., 1981).

Based on physiologically-based pharmacokinetic (PBPK) model, individuals with the highest glutathione-S-transferase activity are predicted to produce about 1.6 times more metabolites than the average individual (Ploemen et al. 1997, Wormhoudt et al. 1996, 1998, IARC 1999). Ploemen et al. (1997) predicted that saturation of the P450 pathway would occur faster in the rat than in humans and that the rat would have a higher turnover of 1,2-dibromoethane from both metabolic pathways than humans and the rat would produce more metabolites (per kg body weight) from both pathways than humans.

In contrast to Ploemen et al. (1997) who considered only the hepatic enzyme activity, Hissink et al. (2000) factored extrahepatic glutathione-S-transferase activity in developing their PBPK model for a 8-hour exposure to 40 ppm in rats and humans. They noted that glutathione-S-transferase, which is found in the kidneys, lungs, stomach, testes, small intestines, and muscle, contributes significantly to the total metabolism of 1,2-dibromoethane. Hissink et al. (2002) made predictions for the average individual with high P450 activity and high glutathione-S-transferase individuals based on the average, low, and high glutathione-S-transferase/P450 ratios. The investigators predicted that the blood concentration of 1,2-dibromoethane and P450 metabolism would be twice as high in the rats as in humans with high P450 activity, because of a higher ventilation rate, cardiac output, and metabolic turnover in rats. Hissink et al. predicted that glutathione-S-transferase activity may account for up to 85% of the loss of 1,2-dibromoethane in the rat, and CYP2E1 accounts for 15-27%, whereas both routes contribute equally to the total amount of metabolites formed in the average individual. The difference between rats and humans is much greater for the glutathione-S-transferase pathway than for the P450 pathway, which constitutes the smaller fraction of metabolism in the rat.

The model suggests that the risk due to glutathione-S-transferase metabolites in the most sensitive humans is much less than for rats. It appears that the rat produces about 4-5 times more P450 metabolites than the most sensitive humans and about 80 times more glutathione-S-transferase metabolites. Individuals with high P450 (low GST) activity produce about two to three times more P450 metabolites than the individual with average or low P450 (high GST) activity. Individuals with low GST (high P450) activity also produced very little GST metabolites compared with individuals with average or high GST activity; the difference is about 10 based on the graph presented by the investigators. Therefore, the production of reactive metabolites varies relative to P450 and GST isoenzymes.

4.2. Mechanism of Toxicity

The metabolism of 1,2-dibromoethane produces two reactive metabolites, both of which bind cellular macromolecules. The metabolites of the cytochrome P450 pathway bind to protein and metabolites of the glutathione-S-transferase pathway bind to DNA. The DNA reactive metabolites are thought to play a role in genetic toxicity and carcinogenicity and the protein reactive metabolites are thought to play a role in cytotoxicity (Wormhoudt, et al. 1998, IARC 1999). Bromine formation during oxidative metabolism may initiate lipid peroxidation in cells, and, thus, contribute to acute toxicity of 1,2-dibromoethane; bromine may(Guha et al., 1993; IARC 1999, U.S. EPA, 2004).

4.3. Structure Activity Relationships

1,2-Dibromoethane is similar in structure to 1,2-dichloroethane. Inhalation exposure to 1,2-dichloroethane produces toxic effects in the respiratory tract, liver, and kidney similar to those of 1,2-dibromoethane (ATSDR 1992).

4.4. Other Relevant Information

4.4.1. Species Variability

Comparing the lethality data for rats and guinea pigs after single inhalation exposures to 1,2-dibromoethane vapor showed that the rat appears to be slightly more sensitive than the guinea pig (Rowe et al. 1952). All 15 guinea pigs exposed to 200 ppm for 7 hour survived, whereas 4 of the 11 rats died after exposure for 7 hours and 3 of 10 rats died after exposure for 5 hours. Similar results were obtained for rats and guinea pigs exposed to 400 ppm of 1,2-dibromoethane vapor.

4.4.2. Susceptible Populations

Wong et al. (1979a) conducted a study in rats to assess the effect of dietary disulfiram on toxicity and carcinogenicity of inhaled 1,2-dibromoethane. Disulfiram, which is an inhibitor of aldehyde dehydrogenase, is used to manage alcohol abuse in humans. It is believed that this substance blocks the oxidation of bromoacetaldehyde (metabolic intermediate of 1,2-dibromoethane) and, therefore, increase the toxicity of 1,2-dibromoethane. Male and female Sprague-Dawley rats were exposed to 20 ppm of 1,2-dibromoethane vapor 7 hours/day, 5 days/week, fed a diet containing 0.05% disulfiram, exposed to 1,2-dibromoethane and fed the treated diet, or received no treatment for 18 months. Disulfiram enhanced the toxicity of inhaled 1,2-dibromoethane. Rats exposed to 1,2-dibromoethane and fed the disulfiram treated diet gained less weight, had a higher mortality rate (all dead by 15 months), and had statistically significantly higher incidences of testicular and prostate atrophy (males only), splenic atrophy, proliferative lesions in the bronchiolar epithelium (females only), hepatocellular carcinoma, and mesenteric hemangiosarcoma. The incidences of bronchogenic carcinoma, kidney adenoma and adenomocarcinoma/carcinoma also were increased in males exposed to 1,2-dibromoethane and fed the disulfiram-treated diet. This study suggests that individuals treated with disulfiram and exposed to 1,2-dibromoethane would be at a potentially higher risk of adverse effects than those exposed to 1,2-dibromoethane alone.

Genetic polymorphism in the cytochrome P450 and glutathione-S-synthetase enzyme systems contributes to the potential variability in the human population with regard to systemic effects of 1,2-dibromoethane and possibly the respiratory effects depending of whether metabolites are responsible for irritation. No data were found on the potential susceptibility of individuals with asthma or variability in children and the elderly.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-time relationship can be developed using log-log regression of the Rowe et al. (1952) data. NIOSH (1977a) calculated LCt_{50} and LCt_{01} values from the Rowe et al. (1952) data. Figure 1 shows the concentration-time relationship based on LC_{50} (or LCt_{50}) values with exposure durations ranging from 2.4 to 720 minutes. The value of n derived from the regression analysis is 1.4. Figure 2 shows the relationship based on LC_{01} values and using the

Rowe et al. (1952) data with exposure concentrations ranging from 200-1600 ppm and exposure durations ranging from 6-120 minutes. It appears that two different mechanism of toxicity may be involved with deaths at the lower concentrations. The value of n derived from the LC_{01} data is 1.4. Figures 3 and 4 show the relationship based on estimations of the exposure time associated "with adverse effects" and "without adverse effects" respectively, at concentrations ranging from 50-800 ppm. The value of n derived from data estimating no adverse effect and adverse effects is 1.6. The exposure duration of the entire data set presented by Rowe et al (1952) ranged from 1.2 minutes at 10,000 ppm to 16 hours at 200 ppm and the log-log regression showed linearity over the entire range. Therefore, AEGL values can be derived by concentration-time extrapolation from 10 minutes to 8 hours.

LC_{50} or LCt_{50} Data

Time	Conc.	Log Time	Log Conc.
2.4	10000	0.3802	4.0000
5.4	5000	0.7324	3.6990
10.8	3000	1.0334	3.4771
18.0	1600	1.2553	3.2041
45.0	800	1.6532	2.9031
120.0	400	2.0792	2.6021
720.0	200	2.8573	2.3010

Regression Output:

Intercept	4.1810
Slope	-0.7087
R Squared	0.9724
Correlation	-0.9861
Degrees of Freedom	5
Observations	7

n = 1.4

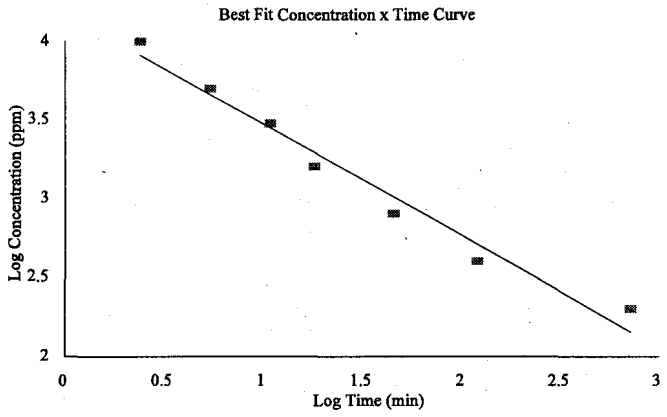

FIGURE 1. Concentrations x time curve for LC_{50} data for rats

LC_{01} or LCt_{01} Data

Time	Conc.	Log Time	Log Conc.
6	1600	0.7782	3.2041
16.8	800	1.2253	2.9031
37.2	400	1.5705	2.6021
120	200	2.0792	2.3010

Regression Output:

Intercept	3.7491
Slope	-0.7051
R Squared	0.9951
Correlation	-0.9975
Degrees of Freedom	3
Observations	5

n = 1.4

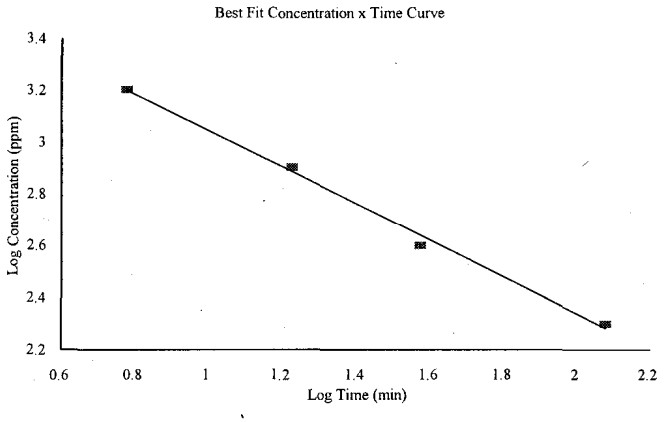

Figure 2. Concentration × time curve for LC_{01} data for rats

Concentrations and Time: Adverse Effects

Time	Conc.	Log Time	Log Conc.
9	800	0.9542	2.9031
60	200	1.7782	2.3010
240	100	2.3802	2.0000

	Regression Output:
Intercept	3.4905
Slope	-0.6391
R Squared	0.9899
Correlation	-0.9949
Degrees of Freedom	1
Observations	3

n = 1.6

1

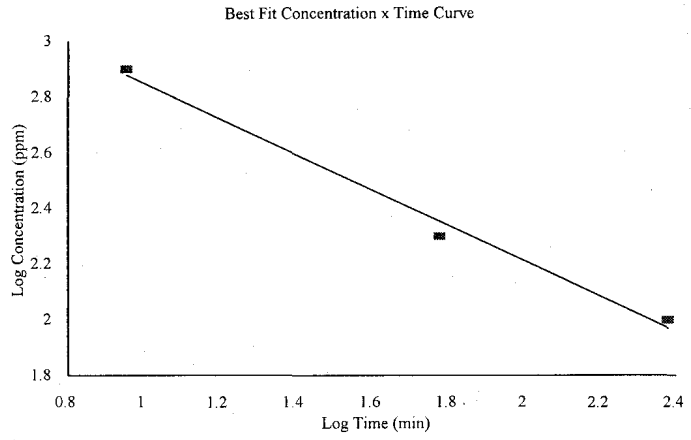

Figure 3. Concentration × time curve for "adverse effects"

2

Concentrations and Time: No Adverse Effects

Time	Conc.	Log Time	Log Conc.
6	800	0.7782	2.9031
42	200	1.6232	2.3010
150	100	2.1761	2.0000
420	50	2.6232	1.6990

	Regression Output:
Intercept	3.3888
Slope	-0.6461
R Squared	0.9973
Correlation	-0.9987
Degrees of Freedom	3
Observations	5

n = 1.6

1

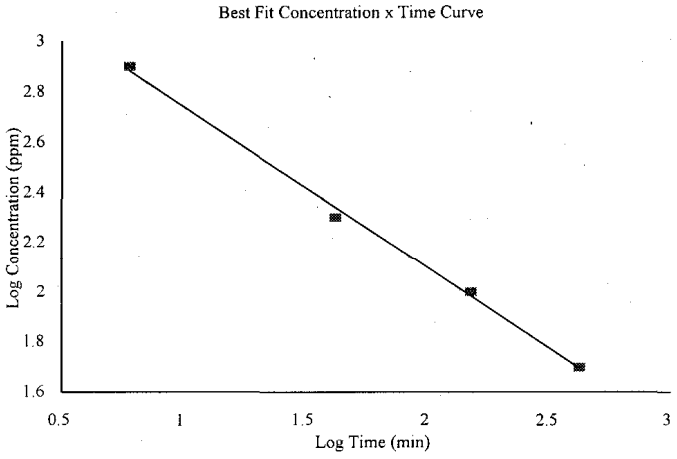

Figure 4. Concentration x time curve for "no adverse effects"

2

4.4.4. Concurrent Exposure Issues

There are no known concurrent exposure issues for 1,2-dibromoethane.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

1,2-Dibromoethane has an unpleasant odor and an odor threshold of 10 ppm. No data were found on the irritation threshold in human. ACGIH (1991) reported serious gastrointestinal and respiratory effects at concentrations ranging from 100 to 200 ppm for durations of 1 hour or less or at 75 ppm for longer durations (not specified). Ott et al. (1980) made a similar report. The lack of specific information precludes using the human data for deriving AEGL-1 values.

5.2. Summary of Animal Data Relevant to AEGL-1

In the acute lethality study using rats, Rowe et al. (1952) reported that exposure of rats to 1,2-dibromoethane at concentrations of 800 ppm for 6 minutes, 200 ppm for 42 minutes, 100 ppm for 2.5 hours, or 50 ppm for 7 hours did not cause adverse effects (toxic injury). Monkeys exposed repeatedly to 25 ppm of 1,2-dibromoethane for 7 hour/day showed no adverse effects after 1 day or after about 31 weeks; however, a concentration of 50 ppm caused ill appearance, nervousness, and unkempt appearance throughout the study (Rowe et al., 1952). The clinical signs suggest a nervous system effect. Nasal and eye irritation were observed in male rats exposed to 1,2-dibromoethane at 10 or 40 ppm, 6 hours/day for 1, 6, or 13 weeks (Nitschke et al., 1980, 1981). It was not possible to determine if nasal lesions occurred after only one exposure.

5.3. Derivation of AEGL-1

AEGL-1 values are derived using the acute inhalation study by Rowe et al. (1952). Adverse effects (liver toxicity) were not associated with exposure to 1,2-dibromoethane at 50, 100, 100, or 800 for 7 hours, 2.5 hours, 42 minutes, and 6 minutes, respectively. The point of departure (POD) selected for AEGL-1 derivation is 50 ppm for 7 hours; this is the lowest concentration and longest duration associated with no adverse effects. The total uncertainty factor is 10 (1 for interspecies sensitivity and 10 for intraspecies variability). An uncertainty factor of 1 is selected for interspecies sensitivity. The effects and mode of action in canines, rodents, non-human primates, and humans exposed to 1,2-dibromoethane are similar, i.e., all species showed similar effects but not necessarily at the same exposure concentrations. PBPK modeling indicated that rats exposed to 1,2-dibromoethane take up about three times more of the substance than humans, and rats produce about five times more active metabolites from the P450 pathway (associated with cytotoxicity) than humans (Ploemen et al. 1997; Hissink et al., 2000). Rats also were predicted to produce about 80 times more GST metabolites than humans (Hissink et al., 2000). The toxic effects of inhaling 1,2-dibromoethane are similar in humans and rats indicating similar pharmacodynamics. The marked difference in metabolite production between rats and humans would overwhelm any difference in pharmacodynamics. Therefore, an interspecies uncertainty factor of 1 is justified. An intraspecies uncertainty factor of 10 was selected because of genetic variability in the metabolism of 1,2-dibromoethane. The PBPK model indicated that production of P450 metabolites ranges about two- to threefold and production of glutathione-S-transferase metabolites ranges about ten fold in the human population. In addition, Wong (1979a) and Igwe et al. (1986) showed that dietary disulfiram (used to manage alcohol abuse in humans) potentiated the toxicity of inhaled 1,2-dibromoethane

in rats. The ten Berge et al. (1986) equation ($C^n \times t = k$) was used to extrapolate to all exposure durations. The value of n = 1.6 was derived by regression analysis of the concentrations and exposure durations associated with no adverse effects reported by Rowe et al. (1952) (See figure 4, Section 4.4.3). The AEGL-1 values are presented in Table 5.

TABLE 5. AEGL-1 Values for 1,2 Dibromoethane

10-min	30-min	1-h	4-h	8-h
52 ppm (400 mg/m^3)	26 ppm (200 mg/m^3)	17 ppm (131 mg/m^3)	7.1 ppm (55 mg/m^3)	4.6 ppm (35 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data on inhalation exposure to 1,2-dibromoethane were reported by Ott et al. (1980), Kochmann (1928), and ACGIH (1991). Concentrations of 75 ppm were reported to be associated with respiratory tract irritation (Ott et al. 1980). The ACGIH (1991) noted that gastrointestinal discomfort, vomiting, and respiratory involvement occurred after exposure to 100 to 200 ppm for 1 hour or less or to 75 ppm for longer durations. Ott et al. (1980) also reported that 75 ppm (no duration provided) was associated with respiratory tract irritation. These reports do not contain sufficient information to verify the concentrations or durations of exposure.

6.2. Summary of Animal Data Relevant to AEGL-2

Rowe et al. (1952) estimated the exposure durations and concentrations (800 ppm for 9 minutes, 200 ppm for 60 minutes and 200 ppm for 240 minutes) associated with adverse effects. These adverse effects included and increase in weight and slight histopathological changes in the liver (not further defined). Rowe et al. (1952) also reported that two rabbits exposed to 100 ppm 1,2-dibromoethane vapor, 7 hours/day for 2 days lost weight and had a slight cloudy swelling in the liver, and exposure of 20 rats to 200 ppm for 1.4 hours resulted in no deaths and appeared unlikely to cause severe effects (Rowe et al. 1952). Monkey exposed to 50 ppm, 7 hours/day for 49 exposures in 70 days exhibited effects indicative of neurotoxicity throughout the study, where as monkeys exposed similarly to 25 ppm showed no effects. Mixed results were obtained from the developmental neurotoxicity studies. The offspring of rats exposed to 65 ppm 1,2-dibromoethane 7 hour/day on GD 10-12 (3 days) showed evidence of neurotoxicity (reduced exploratory activity and peak night activity and lower index of neurobehavioral development) during postnatal development (Vodickova et al. 2003), whereas offspring of rats exposed to 67 ppm 4 hours/day on alternate days 3 days/week showed no signs of neurotoxicity.

6.3. Derivation of AEGL-2

In the acute inhalation study, Rowe et al (1952) noted that rats exposed to 800, 200, or 100 ppm for 9, 60, or 240 minutes, respectively, exhibited adverse effects consisting of an increase in liver weight and slight histopathological changes in the liver (not further defined). These effects are below those defined as AEGL-2 effects (that is, irreversible effects or impaired ability to escape). From these data, a point of departure (POD) for AEGL-2 development is 100 ppm for 4 hours; this is the lowest concentration and longest exposure duration that is associated with slight effects in the liver. The total uncertainty factor was 10: 1 for interspecies sensitivity

and 10 for intraspecies variability. An uncertainty factor of 1 for interspecies sensitivity was selected because the effects and mode of action of 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans,. The toxic effects of inhaling 1,2-dibromoethane are similar in humans and rats. PBPK modeling showed that rats exposed to 1,2-dibromoethane take up about three times more of the substance than humans, and rats produce about five times more active metabolites from the P450 pathway (associated with cytotoxicity) than humans (Ploemen et al. 1997; Hissink et al., 2000). Rats also were predicted to produce about 80 times more GST metabolites than the humans (Hissink et al., 2000). The marked difference in metabolite production between rats and humans would overwhelm any difference in pharmacodynamics. Therefore, an interspecies uncertainty factor of 1 is justified. The rationale for selecting an uncertainty factor of 10 for intraspecies uncertainty is based on the genetic variability associated with the production of P450 and GST metabolites. The PBPK model indicated that production of P450 metabolites ranges about two- to threefold and production of glutathione-S-transferase metabolites ranges about ten fold in the human population. In addition, Wong et al. (1979a) and Igwe et al. (1986) showed that dietary disulfiram (used to manage alcohol abuse in humans) potentiated the toxicity of inhaled 1,2-dibromoethane in rats. Therefore, an intraspecies uncertainty factor of 10 should account for the variability within the human population. The ten Berge et al. (1986) equation ($C^n \times t = k$) was used to extrapolate to all exposure durations. The value of n = 1.6 was derived by regression analysis of the concentrations and time associated with effects considered to be subclinical (See Figure 3, Section 4.4.3). The AEGL-2 values are presented in Table 6.

TABLE 6. AEGL-2 Values for 1,2 Dibromoethane

10-min	30-min	1-h	4-h	8-h
73 ppm (562 mg/m^3)	37 ppm (285 mg/m^3)	24 ppm (185 mg/m^3)	10 ppm (77 mg/m^3)	6.5 ppm (50 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Two humans died after combined inhalation and dermal exposure to 1,2-dibromoethane (Letz et al., 1984) and one died after inhalation exposure (Marmetschke 1910). Clinical signs indicated respiratory tract irritation and pathologic findings indicated damage to the liver, kidneys, and heart (Marmetschke 1910, Letz et al. 1984). Exposure concentrations were not measured in either case.

7.2. Summary of Animal Data Relevant to AEGL-3

Table 2 in Section 3.1.2. summarizes the lethality data from rats exposed to 1,2-dibromoethane at concentrations ranging from 100 ppm to 10,000 for durations ranging from 1.2 minutes to 16 hours and in guinea pigs exposed to 400 ppm for 3 to 7 hours. No deaths occurred among rats after exposure to 100 ppm for 8.5, 12 or 16 hours, 200 ppm for 2 hours, or 400 ppm for 36 minutes or among guinea pigs after exposure to 400 ppm for 2 hours or 200 ppm for 7 hours (Rowe et al. 1952). In the repeat exposure study, Rowe et al. (1952) reported that one of ten rats died after the first exposure to 100 ppm for 7 hours. In light of the observation that no deaths occurred among a total of 60 rats exposed to 100 ppm for 8.5 to 16 hours, the death of one rat after the first exposure to 100 ppm for 7 hours in a repeat exposure study is unlikely to be due to exposure to 1,2-dibromoethane. NIOSH (1977a) reported the LCt_{99}, LCt_{50},

and the LCt_{01} for the data presented by Rowe et al. (1952). The remaining lethality studies in rats were repeat exposure studies. No deaths occurred among guinea pigs exposed to 400 ppm for 2 hours, but deaths occurred in the group exposed to 400 ppm for 3 to 7 hours (Rowe et al., 1952). No rabbits survived after exposure to 100 ppm 1,2-dibromoethane vapor for 7 hours/day for 2 or more days.

7.3. Derivation of AEGL-3

AEGL-3 values were derived using the lethality data based on the concentration and time resulting in no lethality in rats exposed to1,2-dibromoethane (Rowe et al. 1952). None of the 20 rats exposed to 100 ppm of 1,2-dibromoethane for 8.5 hour died during the 3-week observation period. Therefore, the POD is 100 ppm for 8.5 hours. No rats died after exposure to 100 ppm for 12 or 16 hours, but the 8.5-hour duration was selected for AEGL-3 derivation because this time approximated the 8-hour duration for AEGL-derivation. The total uncertainty factor was 10 (1 for interspecies sensitivity and 10 for intraspecies variability). An uncertainty factor of 1 for interspecies sensitivity was selected because the effects and mode of action of 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans. PBPK modeling showed that rats exposed to 1,2-dibromoethane take up about three times more of the substance than humans, and rats produce about five times more active metabolites from the P450 pathway (associated with cytotoxicity) than humans (Ploemen et al. 1997; Hissink et al., 2000). The model also predicted that rats would produce about 80 times more GST metabolites than humans (Hissink et al., 2000). Further, the marked difference in metabolite production between rats and humans would overwhelm any difference in pharmacodynamics. Therefore, an interspecies uncertainty factor of 1 is justified. The data indicate toxicity of inhaled 1,2-dibromoethane is similar in humans and rats. The rationale for selecting an uncertainty factor of 10 for intraspecies uncertainty is based on the genetic variability in the production of P450 and GST metabolites. The PBPK model indicated that production of P450 metabolites of 1,2-dibromoethane ranges about two- to threefold and production of glutathione-S-transferase metabolites ranges about ten fold in the human population. In addition, Wong (1979a) and Igwe et al. (1986) showed that dietary disulfiram (used to manage alcohol abuse in humans) potentiated the toxicity of inhaled 1,2-dibromoethane in rats. Therefore, an intraspecies uncertainty factor of 10 should account for the variability within the human population. The ten Berge et al. (1986) equation ($C^n \times t = k$) was used to extrapolate to all exposure durations. The value of n = 1.4 was derived by regression of LCt_{01} values (same as LC_{01} values) associated with exposure concentrations #1600 ppm (See Figure 2, Section 4.4.3). AEGL-3 values are presented in Table 7.

TABLE 7. AEGL-3 Values for 1,2 Dibromoethane

10-min	30-min	1-h	4-h	8-h
170 ppm (1308 mg/m^3)	76 ppm (585 mg/m^3)	46 ppm (354 mg/m^3)	17 ppm (131 mg/m^3)	10 ppm (77 mg/m^3)

The AEGL-3 values except for the 10-minute value are below the IDLH of 100 ppm.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL-1 values were derived from a concentration (50 ppm) and exposure duration (7 hours) that were not associated with adverse effects in rats. AEGL-2 values were derived from an estimate of the duration of exposure (4 hours) at 100 ppm that was associated with slight liver histopathology in rats. AEGL-3 values were derived from the highest concentration that did not cause death in rats after a exposure to 100 ppm of 1,2-dibromoethane for 8.5 hours or more. The interspecies uncertainty factor of 1 was selected for interspecies extrapolation because PBPK modeling indicated that 1,2-dibromoethane levels in blood and the production of P450 and GST metabolites are higher in rats than in humans; in addition, the lethality studies did not show major differences between the effects of inhaled 1,2-dibromoethane in humans and rats. The uncertainty factor of 10 for intraspecies variability was based on the differences in production of metabolites in humans with high and low enzyme levels and the increased sensitivity of individuals taking therapeutic doses of disulfiram. The AEGL values are summarized in Table 8.

TABLE 8. Summary of AEGL Values

Classification	Exposure Duration					
	10-min	30-min	1-h	4-h	8-h	Endpoint/Reference
AEGL-1 (Nondisabling)	52 ppm (400 mg/m^3)	26 ppm (200 mg/m^3)	17 ppm (131 mg/m^3)	7.1 ppm (55 mg/m^3)	4.6 ppm (35 mg/m^3)	No adverse effect (Rowe et al., 1952)
AEGL-2 (Disabling)	73 ppm (562 mg/m^3)	37 ppm (285 mg/m^3)	24 ppm (185 mg/m^3)	10 ppm (77 mg/m^3)	6.5 ppm (50 mg/m^3)	Slight histopathological changes in the liver; no-effect-level for irreversible toxicity or impaired ability to escape (Rowe et al., 1952)
AEGL-3 (Lethal)	170 ppm (1308 mg/m^3)	76 ppm (585 mg/m^3)	46 ppm (354 mg/m^3)	17 ppm (131 mg/m^3)	10 ppm (77 mg/m^3)	no effect level for lethality (Rowe et al. 1952)

8.2. Comparison with Other Standards and

Extant standards and guidelines are summarized in Table 9. ERPG values have not been derived for 1,2-dibromoethane. The IDLH of 100 ppm was based on inhalation toxicity data in humans (Ott et al., 1980) and animal data of Rowe et al. (1952). All AEGL values are below the IDLH of 100 ppm except for the AEGL-3 value for a 10-minute exposure.

TABLE 9. Extant Standards and Guidelines for 1,2 Dibromoethane

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	52 ppm (400 mg/m^3)	26 ppm (200 mg/m^3)	17 ppm (131 mg/m^3)	7.1 ppm (55 mg/m^3)	4.6 ppm (35 mg/m^3)
AEGL-2	73 ppm (562 mg/m^3)	37 ppm (285 mg/m^3)	24 ppm (185 mg/m^3)	10 ppm (77 mg/m^3)	6.5 ppm (50 mg/m^3)
AEGL-3	170 ppm (1308 mg/m^3)	76 ppm (585 mg/m^3)	46 ppm (354 mg/m^3)	17 ppm (131 mg/m^3)	10 ppm (77 mg/m^3)
PEL-TWA (OSHA)[a]	20 ppm (8-hr TWA)				
PEL-STEL (OSHA)[b]	30 ppm (ceiling); 50 ppm (5-minute peak)				
IDLH (NIOSH)[c]	100 ppm				
REL-TWA (NIOSH)[d]	0.045 ppm (carcinogenicity)				
REL-STEL (NIOSH)[e]	0.13 ppm (15 minutes)				
TLV-TWA (ACGIH)[f]	none, animal carcinogen				
TLV-STEL (ACGIH)[g]	none				
MAK (Germany)[h]	none, carcinogen category 2				
MAK Peak Limit (Germany)[i]	none				

[a]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1999) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[b]**OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** (OSHA 1999) is defined analogous to the ACGIH-TLV-STEL.

[c]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1994) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2003) is defined analogous to the ACGIH-TLV-TWA.

[e]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 2003) is defined analogous to the ACGIH TLV-STEL.

[f]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2003) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[g]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2003) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[h]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft (German Research Association 2002) is defined analogous to the ACGIH-TLV-TWA.

[i]**MAK Spitzenbegrenzung (Peak Limit [give category])** (German Research Association 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

8.3. Data Adequacy and Research Needs

1,2-Dibromoethane is carcinogenic at multiple sites in two rodent species; therefore, human studies should not be conducted with this substance. Data were not available for deriving AEGL-1 values and based on the AEGL-2 values, any values derived for AEGL-1 would be below the irritation threshold. The confidence in the AEGL-2 values could be improved with a single exposure study designed specifically to investigate non-lethal effects. AEGL-3 values were based on a robust data set, which is considered adequate for deriving these values.

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APPENDIX A: Derivation of AEGL Values

AEGL-1

Key Studies:	Rowe et al., 1952
Toxicity endpoints:	No adverse effects in rats exposed to 50 ppm for 7 hours
Time scaling	ten Berge's equation: $C^n \times t = k$, where n = 1.6 derived from exposure concentrations and durations associated with no adverse effects in rats
Uncertainty factors:	Total = 10 1, interspecies 10, intraspecies
Modifying factor:	1
Calculations:	
1-h exposure (expt.)	C = 50 ppm/10 (uncertainty factor) = 5.0 ppm $C^n \times t = k$; n = 1.6 C = 5.0 ppm, t = 420 min k = 1514 ppm•min
10-minute AEGL-1	$C = (k/t)^{1/1.6} = (5516 \text{ ppm•min}/10 \text{ min})^{1/1.6} = 52$ ppm C = 52 ppm
30-minute AEGL-1	$C = (k/t)^{1/1.6} = (5516 \text{ ppm•min}/30 \text{ min})^{1/1.6} = 26$ ppm C = 26 ppm
1-hour AEGL-1	$C = (k/t)^{1/1.6} = (5516 \text{ ppm•min}/60 \text{ min})^{1/1.6} = 17$ ppm C = 17 ppm
4-hour AEGL-1	$C = (k/t)^{1/1.6} = (5516 \text{ ppm•min}/240 \text{ min})^{1/1.6} = 7.1$ ppm C = 7.1 ppm
8-hour AEGL-1	$C = (k/t)^{1/1.6} = (5516 \text{ ppm•min}/480 \text{ min})^{1/1.6} = 4.6$ ppm C = 4.6 ppm

AEGL-2

Key Studies:	Rowe et al., 1952
Toxicity endpoints:	Increase in liver weight and slight histopathological changes in the liver (not further defined by the authors of the study). These effects are less severe than those defined as AEGL-2 effects (irreversible effects or impaired ability to escape).
Time scaling	ten Berge's equation: $C^n \times t = k$, where n = 1.6 derived from exposure concentrations and durations associated with adverse effects (liver toxicity) in rats.
Uncertainty factors:	Total = 10 1, interspecies 10, intraspecies
Modifying factor:	1
Calculations:	
1.4-h exposure (expt.)	C = 100 ppm/10 (uncertainty factor) = 10 ppm $C^n \times t = k$; n = 1.6 C = 10 ppm, t = 240 min k = 9555 ppm•min
10-minute AEGL-2	$C = (k/t)^{1/1.6} = (9555 \text{ ppm•min}/10 \text{ min})^{1/1.6} = 73$ ppm C = 73 ppm
30-minute AEGL-2	$C = (k/t)^{1/1.6} = (9555 \text{ ppm•min}/30 \text{ min})^{1/1.6} = 37$ ppm C = 37 ppm
1-hour AEGL-2	$C = (k/t)^{1/1.6} = (9555 \text{ ppm•min}/60 \text{ min})^{1/1.6} = 24$ ppm C = 24 ppm
4-hour AEGL-2	$C = (k/t)^{1/1.6} = (9555 \text{ ppm•min}/240 \text{ min})^{1/1.6} = 10$ ppm C = 10 ppm
8-hour AEGL-2	$C = (k/t)^{1/1.6} = (9555 \text{ ppm•min}/480 \text{ min})^{1/1.6} = 6.5$ ppm C = 6.5 ppm

AEGL-3

Key Studies:	Rowe et al. 1952
Toxicity endpoint:	highest concentration without lethality for 8.5 hours or more
Time scaling	ten Berge's equation: $C^n \times t = k$, where n = 1.4 derived from rat LC_{01} (LCt_{01}) data for exposure concentrations ranging from 200-1600 ppm and durations ranging from 6-120 minutes
Uncertainty factors:	Total = 10 1, interspecies 10, intraspecies
Modifying factor:	1
8.5-h exposure (expt.)	C = 100 ppm/10 (uncertainty factor) = 10 ppm $C^n \times t = k$; n = 1.4 C = 10 ppm, t = 510 min k = 12,811 ppm℃min
10-minute AEGL-3	$C = (k/t)^{1/1.4} = (12{,}811 \text{ ppm℃min}/10 \text{ min})^{1/1.4} = 166$ ppm C = 170 ppm
30-minute AEGL-3	$C = (k/t)^{1/1.4} = (12{,}811 \text{ ppm℃min}/30 \text{ min})^{1/1.4} = 76$ ppm C = 76 ppm
1-hour AEGL-3	$C = (k/t)^{1/1.4} = (12{,}811 \text{ ppm℃min}/60 \text{ min})^{1/1.4} = 46$ ppm C = 46 ppm
4-hour AEGL-3	$C = (k/t)^{1/1.4} = (12{,}811 \text{ ppm℃min}/240 \text{ min})^{1/1.4} = 17$ ppm C = 17 ppm
8-hour AEGL-3	$C = (k/t)^{1/1.4} = (12{,}811 \text{ ppm℃min}/480 \text{ min})^{1/1.4} = 10$ ppm C = 10 ppm

APPENDIX B: Carcinogenicity Assessment

Long-term studies have demonstrated that inhalation exposure to 1,2-dibromoethane induces neoplasms in mice and rats. 1,2-dibromoethane induced tumors in multiple organs/tissues in two species. Neoplasms developed in the lungs/bronchus and nasal cavity or male mice and in the lungs/ bronchus, nasal cavity, and circulatory system, subcutaneous tissue, and mammary gland in female mice. Neoplasms developed in the nasal cavity, spleen, adrenal gland, tunica vaginalis, and subcutaneous tissue of male rats and nasal cavity, lungs/bronchus, circulatory system, and mammary gland of female rats. The carcinogenicity data are summarized in Table 4. EPA concluded that 1,2-dibromoethane is "likely to be carcinogenic to humans" based on strong evidence of carcinogenicity in animals and inconclusive evidence of carcinogenicity in an exposed human population (U.S. EPA, 2004). The unit risk calculated using data from male rats reported by NTP (1982) is 6×10^{-4} (Fg/m^3)$^{-1}$ or 6×10^{-1} mg/m^3)$^{-1}$ (95% upper bound) (U.S. EPA, 2004). The exposure concentrations were adjusted for discontinuous exposure.

Data summary (NTP, 1982): Groups of 50 male Fisher 344 rats were exposed to 0, 10, or 40 ppm, 6 hours/day, 5 days/week for 104, 103, or 88 weeks, respectively. Nasal cavity tumors developed in 1/46, 39/45, and 41/43 rats, respectively; hemangiosarcoma developed in 0/46, 1/43, and 15/28 rats, respectively; and mesotheliomas developed in 1/46, 8/43, and 25/35 rats respectively.

The calculations for AEGL values following the method presented by NRC (1986a) are presented below.

To calculate a "virtually safe dose" (VSD of d) at a cancer risk of 10^{-4}:

$$d = 10^{-4}/(6 \times 10^{-1}\ (mg/m^3))^{-1} = 1.67 \times 10^{-4}\ mg/m^3$$

To calculate the total cumulative dose for a total lifetime exposure of 70 years, which is equivalent to 25,600 days:

$$\text{total } d = d \times 25{,}600 = 1.67 \times 10^{-4}\ mg/m^3 \times 25{,}600 = 4.27\ mg/m^3$$

Adjustment to allow for uncertainties in assessing potential cancer risks under short-term exposures under the multistage model (Crump and Howe, 1984) the total dose is divided by a factor of 6:

$$4.27\ mg/m^3/6 = 7.1 \times 10^{-1}\ mg/m^3 = 71\ mg/m^3 = 9.2\ ppm.$$

Therefore, a single exposure to 1,2-dibromoethane at 9.2 ppm for 24 hours would represent a cancer risk of 10^{-4}.

$c^n \times t = k$, where c = concentration, n = 1, t = time, and k is a constant.
k = (9.2 ppm) × 24 hours = 13248 ppmCmin

To calculate the exposure concentration for other time frames, rearrange the equation as follows:

c = k/t, where, t = 10 min, 30 min (0.5 h) or 1, 4, or 8 h

24-h = 9.2 ppm (71 mg/m^3).

The AEGL values for 0.5, 1, 4, and 8 hours are presented below for risks of 10^{-4}, 10^{-5}, and 10^{-6}.

Time (h)	10^{-4}	10^{-5}	10^{-6}
0.5	440	44.0	4.40
1	220	22.0	2.20
4	55	5.50	0.55
8	25	2.50	0.25

These values based on carcinogenicity exceed the AEGL values based on lethality data and are not proposed for AEGL-2 or 3.

APPENDIX C: Derivation Summary for 1,2-Dibromoethane AEGLs

1

AEGL-1 VALUES for 1,2–Dibromoethane				
10-min	**30-min**	**1-h**	**4-hr**	**8-h**
52 ppm (400 mg/m^3)	**26 ppm (200 mg/m^3)**	**17 ppm (131 mg/m^3)**	**7.1 ppm (55 mg/m^3)**	**4.6 ppm (35 mg/m^3)**
Key Reference: Rowe et al., 1952				
Test Species/Strain/Number: rats/strain not specified/10 females				
Exposure Route/Concentrations/Durations: inhalation/50, 100, 200, and 800 ppm for 420, 150, 42, and 6 minutes, respectively				
Effects: No adverse effects associated with exposure to 50, 100, 200, or 800 ppm for 420, 150, 42, and 6 minutes, respectively				
Endpoint/Concentration/Rationale: No adverse effects in rats at 50 ppm for a 420-minute (7-hour) exposure				
Uncertainty Factors/Rationale: Total uncertainty factor:10 Interspecies: 1 The effects and mode of action of 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans. PBPK modeling indicates that rats produce up to 80 times more active metabolites than humans, which would overwhelm any differences in pharmacodynamics Intraspecies: 10 PBPK modeling indicates that humans vary by a factor of about 10 in the production of reactive metabolites, and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane.				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: : $C^n \times t = k$, where n = 1.6 based on regression of exposure concentrations and durations not associated with adverse effects				
Data Adequacy: The data for deriving AEGL-1 values were very limited; the report did not include some important details regarding the methods and results.				

2

1

AEGL-2 VALUES for 1,2–Dibromoethane				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
73 ppm (562 mg/m^3)	**37 ppm (285 mg/m^3)**	**24 ppm (185 mg/m^3)**	**10 ppm (77 mg/m^3)**	**6.5 ppm (50 mg/m^3)**
Key Reference: Rowe et al., 1952				
Test Species/Strain/Number: Rat/unknown strain/10 females/group				
Exposure Route/Concentrations/Durations: inhalation, 100, 200, and 800 ppm for 240, 60, and 9 minutes				
Effects: Effects in rats (increased weight and slight histopathological changes in the liver) at each concentration and associated exposure duration				
Endpoint/Concentration/Rationale: Adverse effects that are expected to be subclinical in humans/50 ppm for 240 minutes				
Uncertainty Factors/Rationale: Total uncertainty factor:10 Interspecies: 1 The effects and mode of action of 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans. PBPK modeling indicates that rats produce up to 80 times more active metabolites than humans, which would overwhelm any differences in pharmacodynamics Intraspecies: 10 PBPK modeling indicates that humans vary by a factor of about 10 in the production of reactive metabolites., and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: $C^n \times t = k$, where n = 1.6 based on regression of exposure concentrations and durations associated with adverse effects in rats likely to be subclinical in humans.				
Data Adequacy: The data for deriving AEGL-2 values were very limited; the report did not include some important details regarding the methods and results.				

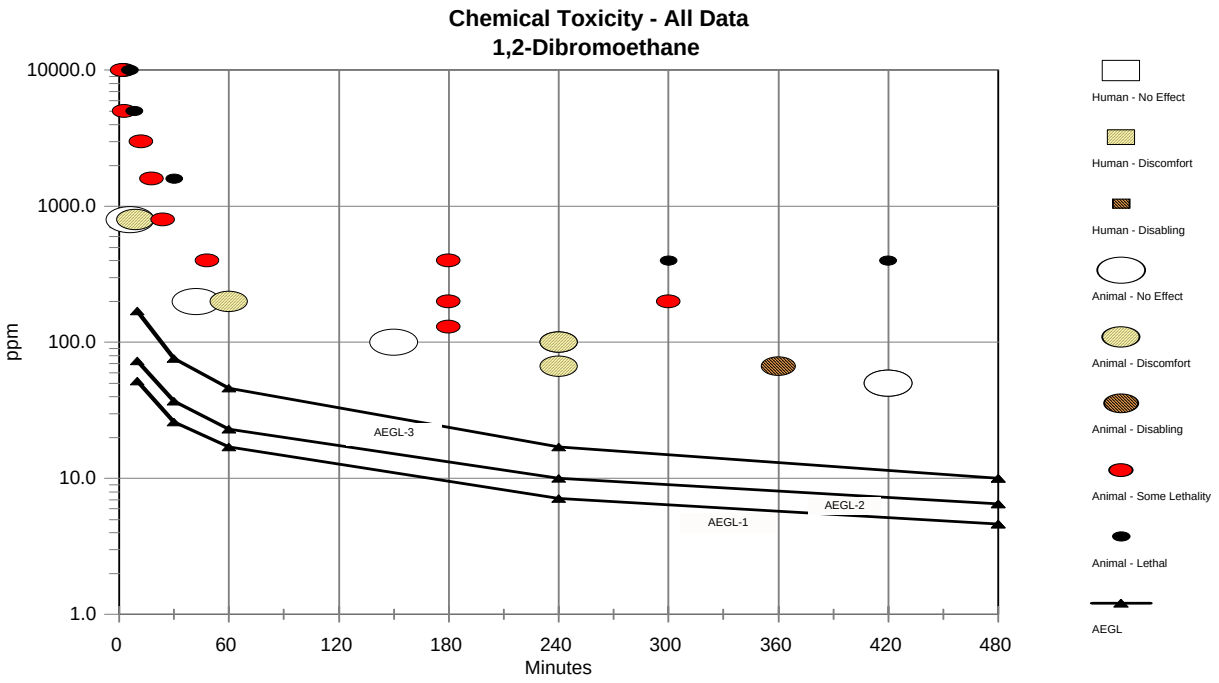
2

1

AEGL-3 VALUES for 1,2–Dibromoethane				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
170 ppm ($1308\ mg/m^3$)	76 ppm ($585\ mg/m^3$)	46 ppm ($354\ mg/m^3$)	17 ppm ($131\ mg/m^3$)	10 ppm ($77\ mg/m^3$)
Key Reference: Rowe et al. 1952				
Test Species/Strain/Number: rat/strain was not reported/4-20 animals/group				
Exposure Route/Concentrations/Durations: inhalation/100-10,000 ppm for 1.2 minutes to 16 hours				
Effects: death occurred at all exposure concentrations except 100 ppm, but not all exposure durations. Deaths within the first 24 hours were attributed to cardiac and respiratory failure, later deaths were attributed to secondary pneumonia. Rats that died lost weight showed evidence of upper and lower respiratory tract irritation. Microscopic findings included severe pulmonary damage, degeneration and necrosis in the liver, and congestion and edema in the kidney tubules 16-24 hours after exposure.				
Endpoint/Concentration/Rationale: 100 ppm for 8.5 hours; no effect level for lethality. Although the no-effect levels extended to 12 and 16 hours at 100 ppm, the 8.5 hour duration was selected for the POD because it approximates the exposure duration for the AEGL values.				
Uncertainty Factors/Rationale: Total uncertainty factor:10 Interspecies: 1 The effects and mode of action of 1,2-dibromoethane appear to be similar across species including canine, rodents, non-human primates, and humans. PBPK modeling indicates that rats produce up to 80 times more active metabolites than humans, which would overwhelm any differences in pharmacodynamics Intraspecies: 10 PBPK modeling indicates that humans vary by a factor of about 10 in the production of reactive metabolites., and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane.				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: $C^n \times t = k$, where n = 1.4 based on regression of LC_{01} values for exposure duration ranging from 6-120 minutes at concentrations ranging from 1600 down to 200 ppm.				
Data Adequacy: A very detailed acute inhalation exposure study was available with exposure concentrations ranging from 200 to 10,000 ppm and exposure duration ranging from 0.6 minutes to 16 hours. LCt values were calculated for each exposure concentration.				

2

APPENDIX D: Category Plot for Dibromoethane


Chemical Toxicity - All Data
1,2-Dibromoethane
10000.0
1000.0
100.0
10.0
1.0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

1
2