TOXICITY SUMMARY FOR ETHYLENE DIBROMIDE

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EXECUTIVE SUMMARY

Ethylene dibromide (EDB) is a colorless, water soluble liquid that has been used as a pesticide and gasoline additive (U.S. EPA 1984). Due to increased EPA regulations and restrictions, both uses have declined in the United States (ATSDR, 1992). Currently, it is used as a chemical intermediate and special solvent (Torkelson, 1994). EDB has been identified in the atmosphere near manufacturing sites, gasoline stations, urban high-traffic areas, and rural sites; in various effluent streams and runoff water, groundwater, surface water, and in drinking water; in soils from fumigation centers; and in food samples (U.S. EPA, 1984). EDB partitions to the atmosphere and groundwater. In the atmosphere, it can be transported over long distances. It is very mobile in soils and can be biodegraded in soils. Because of its high water solubility, EDB is not expected to bioconcentrate or to biomagnify in the food chain (ATSDR, 1992).

EDB can be absorbed through the lungs, digestive tract, and skin (Jakobson et al., 1982; Plotnick et al., 1979; Watanabe et al., 1977). EDB is extensively metabolized in various tissues to 2-bromoacetaldehyde as well as to other toxic metabolites. Excretion occurs primarily in the urine (Plotnick et al., 1979; Plotnick and Conner, 1976).

In humans, ingestion of lethal (4.5 mL) or sublethal amounts of EDB has caused vomiting, watery diarrhea, anuresis, oropharyngeal ulceration, gastric mucosal erosion, massive liver and kidney damage, depression, disorientation, and collapse (Olmstead, 1960; Saraswat et al., 1986).

Animal studies indicate that the primary target organs following chronic oral exposure are the forestomach and reproductive system. Lesions of the forestomach lining (acanthosis and hyperkeratosis of the squamous epithelium) and testicular atrophy were observed in rodents exposed to 37-41 mg/kg/day, 5 days/week for 53-61 weeks. Also observed were mild liver lesions (NCI, 1978). Antispermatogenic effects occurred in bulls administered 2-4 mg/kg/day for 14-16 months day (Amir and Ben-David, 1973; Amir and Volcani, 1965) and decreased egg production was reported in hens fed EDB (Bondi et al., 1955). An oral Reference Dose (RfD) for EDB has not been derived.

Acute inhalation and/or dermal exposure to high concentrations of EDB has resulted in mucous membrane irritation, central nervous system (CNS) depression, metabolic acidosis, liver and kidney damage, and death in humans (Torkelson, 1994; Letz et al., 1984). Occupational exposure to EDB has produced decreased sperm counts in manufacturing and agricultural workers (Ter Haar, 1980; Takahashi et al. 1981; Ratcliffe et al., 1987). Reddening, blistering, and burning pain was reported following prolonged dermal contact (Torkelson, 1994). An inhalation Reference Concentration (RfC) of 2E-3 mg/m^3 for subchronic and 2E-4 mg/m^3 for chronic exposure to EDB was calculated based on a lowest-observed-adverse-effect level (LOAEL) of 88 ppb from an occupational exposure study with papaya workers exposed to EDB as a fumigant (Ratcliffe et al., 1987; Schrader et al., 1988). Male reproductive toxicity was identified as the critical effect. The RfC is currently under review by EPA (U.S. EPA, 1995).

In animals, inhalation of high concentrations of EDB for short time periods has produced lung, liver, and kidney lesions. The maximum survival times for rats exposed by inhalation to EDB vapor ranged from 6 minutes at 3000 ppm (23,040 mg/m^3) to 2 hours at 200 ppm (1536 mg/m^3) (Rowe et al., 1952). Target organs following inhalation of EDB for prolonged periods are the nasal cavity, kidneys, liver, and reproductive/developmental systems. Subchronic/chronic inhalation exposure produced lesions in the respiratory tract, particularly the nasal cavity, increased liver and kidney weights, and toxic nephropathy at $40 ppm (307 mg/m^3) (Nitschke et al., 1982; NTP, 1982). Testicular atrophy and degeneration was observed in rats following inhalation of 10 ppm (77 mg/m^3), 6 hours/day, 5 days/week for two years (NTP, 1982). Exposure during gestation to concentration up to 80 ppm (614 mg/m^3) induced fetotoxic effects in rats (skeletal anomalies) and mice (increased resorptions and reduced fetal body weight) at maternally toxic doses (Short et al., 1978).

Epidemiological studies are inadequate to determine if a correlation exists between exposure to EDB and increased cancer risk in humans. Carcinogenicity bioassays using rats and mice have shown that EDB induces tumors at the site of contact and at distant sites following oral, inhalation, and dermal exposures. Following oral administration, EDB induced squamous cell carcinomas of the forestomach in

both sexes of rats and mice; alveolar/bronchiolar lung tumors in male and female mice; liver carcinomas in female rats; hemangiosarcomas in male rats; alveolar/bronchiolar adenomas in mice; and esophageal papillomas/carcinomas in female mice (NCI, 1978; Van Duuren, 1985, 1986). Following inhalation, EDB induced adenomas and carcinomas of the nasal cavity in rats and mice; hemangiosarcomas of the spleen and abdominal retroperitoneum in rats and mice, respectively; subcutaneous fibrosarcomas in mice; mammary tumors in female rats and mice; mesotheliomas of the tunica vaginalis in male rats; and alveolar/bronchiolar lung tumors in rats and mice (NTP, 1982; Stinson et al., 1981). The chemical also induced skin and lung tumors after dermal application (Van Duuren et al., 1979).

EDB was assigned by EPA to weight-of-evidence group B2, probable human carcinogen. Group B2 includes chemicals for which evidence for carcinogenicity is adequate in animals but inadequate in humans. For oral exposure, the slope factor is 8.5 $(mg/kg/day)^{-1}$ and the unit risk is 2.5E-3 $(\mu g/L)^{-1}$ (U.S. EPA, 1996). The inhalation slope factor and unit risk are 7.6E-1 $(mg/kg/day)^{-1}$ (U.S. EPA, 1995) and 2.2E-4 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1996), respectively.

1. INTRODUCTION

Ethylene dibromide (CAS No. 106-93-4), also known as 1,2-dibromoethane or EDB, is a colorless, nonflammable liquid with a molecular weight of 187.9 and a chemical formula of CH_2BrCH_2Br. It has a boiling point of 131.6°C, a melting point of 9.97°C, a density of 2.19 g/mL at 20°C, and a vapor pressure of 11 mm Hg at 25°C. It is soluble in water, alcohol, and ether. EDB is manufactured by the addition of bromide to ethylene (U.S. EPA, 1984). EDB may be formed naturally in the ocean as a result of macro algae growth (HSDB, 1996). EDB has been used extensively in leaded antiknock gasoline and as a fumigant for grains, fruits, and vegetables (U.S. EPA, 1984). Due to the increased regulation of leaded gasoline and the EPA's ban in 1984 on the use of EDB as a soil and grain fumigant, the production and consumption in the United States has declined significantly (ATSDR, 1992). It is still used in a minor capacity as a chemical intermediate, special solvent, gauge fluid, and insect control (ATSDR, 1992; Torkelson, 1994).

Historically, EDB has been released to the environment mainly as the result of its use as a gasoline additive and fumigant (ATSDR, 1992). EDB has been identified in the atmosphere at manufacturing sites, gasoline stations, urban high-traffic areas, and rural sites. It also has been identified in various effluent streams and runoff water, groundwater, surface water, and drinking water; in soils from fumigation centers; and in food samples (U.S. EPA, 1984). EDB partitions to the atmosphere and groundwater. It can be transported over long distances in the atmosphere, and is very mobile in soils. It is transformed in the atmosphere by reaction with hydroxyl radicals and in soils by biodegradation. Because of its high water solubility, EDB is not expected to bioconcentrate or to biomagnify in the food chain. The chemical has been identified in the United States at several hazardous waste sites on the National Priority List (NPL). For the general population, the most important route of exposure is ingestion of contaminated drinking water (ATSDR, 1992).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

EDB is absorbed by the oral, inhalation, and dermal routes of exposure. Deaths resulting from suicide attempts by ingestion of EDB (Olmstead, 1960; Saraswat et al., 1986) suggest that oral absorption occurs in humans. It can be inferred that absorption from the gastrointestinal tract is extensive in rats, because 73% of a 15 mg/kg gavage dose was excreted in the urine and 2% was excreted in the feces within 48 hours (Plotnick et al., 1979). Blood levels of EDB in rats during and following inhalation of 78 ppm (600 mg/m^3) for 6 hours rose quickly and then leveled off within the first hour of exposure (Watanabe et al., 1977). Following dermal exposure of 1 mL EDB under occlusion for 6 hours, a similar rise in blood concentration was observed in guinea pigs (Jakobson et al., 1982).

2.2. DISTRIBUTION

Kidney and liver lesions following intentional ingestion of EDB by humans are indirect evidence of distribution to these organs (Olmstead, 1960). Twenty four hours after administration of 15 mg/kg radiolabeled EDB by gavage to rats, 3% of the radioactivity was detected in fat, brain, kidney, liver, spleen, testes, and blood. By 48 hours, 1.1% of the dose was found in the liver (Plotnick et al., 1979). The highest levels of radioactivity were found in the kidneys and liver of rats following inhalation exposure to 7-75 ppm (54-576 mg/m^3) of radiolabeled EDB (Watanabe et al., 1977). After intraperitoneal administration of radiolabeled EDB to guinea pigs (30 mg/kg), the highest concentrations of radioactivity were found in the liver, kidneys, and adrenals (Plotnick and Conner, 1976).

2.3. METABOLISM

EDB is rapidly and extensively metabolized in various tissues of animals through microsomal oxidation by cytochrome P-450 forming 2-bromoacetaldehyde, a metabolite that can produce liver damage by binding to cellular proteins. 2-Bromoacetaldehyde can be further metabolized by aldehyde dehydrogenase to 2-bromoethanol (a highly toxic and genotoxic compound) or it can be metabolized by aldehyde dehydrogenase to bromoacetic acid which is excreted in the urine. In addition, 2-bromoacetaldehyde can be conjugated with glutathione. The conjugated metabolite is reduced to *S*-

carboxymethylglutathione. The latter can form *S*-carboxymethylcysteine which can be metabolized to thioglycolic acid and excreted in the urine. Alternately, *S*-carboxymethyl-glutathione can be metabolized to *S*-($-hydroxyethyl)cysteine and excreted in the urine as a mercapturic acid conjugate (ATSDR, 1992).

2.4. EXCRETION

Following oral administration of EDB, rats excreted about 73% of the dose in the urine, (primarily as mercapturic acid derivatives); fecal excretion accounted for 3% of the administered dose (Plotnick et al., 1979). After intraperitoneal administration of radiolabeled EDB to guinea pigs (30 mg/kg), 65% of the dose was excreted as urinary metabolites and 12% was excreted unchanged in the expired air (Plotnick and Conner, 1976).

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Symptoms in an adult female who died two days after ingestion of 4.5 mL EDB included recurrent vomiting, watery diarrhea, anuresis, depression, disorientation, and collapse. At autopsy, massive hepatic centrilobular necrosis and proximal tubular epithelial damage of the kidneys were noted (Olmstead, 1960). Two of six teenagers or young adults died after intentional ingestion of EDB (dose not given). Pathological findings included oropharyngeal ulceration, gastric mucosal erosion, massive hepatocellular necrosis, icterus, and renal lesions (Saraswat et al., 1986).

3.1.1.2. Animal

Rowe et al. (1952) reported the following oral LD_{50}s: 146 mg/kg, male rats; 117 mg/kg, female rats; 420 mg/kg, female mice; 110 mg/kg, guinea pigs; 55 mg/kg, female rabbits; and 79 mg/kg, chickens.

A single gavage dose of 110 mg/kg to rats produced centrilobular dilatation of the liver within 8 hours, hepatocellular degeneration within 17 hours, and centrilobular necrosis 22 hours after exposure (Broda et al., 1976). Administration of 40 or 80 mg/kg/day by gavage for 2 weeks produced forestomach mucosal cell proliferation and hyperkeratosis in rats (Ghanayem et al., 1986).

3.1.2. Subchronic Toxicity

Information on the subchronic toxicity of EDB in humans or animals following oral exposure was not available.

3.1.3. Chronic Toxicity

3.1.3.1. Human

Information on the chronic toxicity of EDB in humans following oral exposure was not available.

3.1.3.2. Animal

In a cancer bioassay by NCI (1978), male and female Osborne-Mendel rats were treated by gavage with EDB in corn oil 5 times/week at time-weighted-average (TWA) doses of 38 or 41 mg/kg/day for 49 weeks (males) and 37 or 39 mg/kg/day (females) for 61 weeks (see also Sections 3.1.4.2. and 4.1.2). $B6C3F_1$ mice received TWA doses of 62 or 105 mg/kg/day for 53 weeks. [Note: High mortality as a result of incorrect determination of the maximum tolerated dose prompted alterations in the dosing regimen, resulting in similar TWA doses for the low and high dose groups of rats and an early termination of the study. Periodic dose adjustments were made for mice]. In addition to early mortality in rats and mice, other effects included weight decreases in both species; acanthosis and hyperkeratosis of the forestomach squamous epithelium in high-dose rats and mice; liver effects (peliosis hepatis) in male rats; and adrenal cortical degeneration in a small number of male and female rats.

3.1.4. Developmental and Reproductive Toxicity
3.1.4.1. Human

Information on the developmental or reproductive toxicity of EDB in humans following oral exposure was not available.

3.1.4.2. Animal

In a NCI (1978) bioassay (see Sections 3.1.3.2. and 4.1.2.), the incidence of testicular degeneration was not increased in treated rats; however, testicular degeneration occurred at an earlier age compared with controls. Testicular atrophy occurred in mice at the high dose (TWA 105 mg/kg/day).

A high percentage (up to 79%) of abnormal spermatozoa in bull ejaculates was reported as early as two weeks following oral administration of 10 doses of 4 mg/kg EDB on alternate days (Amir and Ben-David, 1973). Bull calves were fed 2 mg/kg/day EDB from age 4 days to 12 months, and at 12 months of age the bulls were administered 4 mg/kg in gelatin capsules every other day until they were 14-16 months of age. Treatment with EDB resulted in decreased semen density, decreased sperm motility, and morphological alterations of spermatozoa (Amir and Volcani, 1965).

Adult hens maintained on feed containing 50-320 mg/kg EDB laid smaller eggs; after 6 weeks on the diet containing the highest dose, egg laying ceased irreversibly (Bondi et al., 1955).

3.1.5. Reference Dose

An oral Reference Dose (RfD) for EDB has not been derived.

3.2. INHALATION EXPOSURES
3.2.1. Acute Toxicity
3.2.1.1. Human

Inhalation exposure as well as dermal exposure to EDB may have played a role in the death of two pesticide workers exposed to EDB (Letz et al., 1984; see also Section 3.3.1.1). Exposure to unspecified high concentrations of EDB vapors may result in some central nervous system (CNS) depression, although the anesthetic action is weak (Torkelson, 1994). Vapor concentrations which are anesthetic are highly irritating to the mucous membranes. Several cases of poisoning have resulted from attempts to use EDB as an anesthetic in the belief it was ethyl bromide (ACGIH, 1991).

3.2.1.2. Animal

Rowe et al. (1952) determined the following maximum survival times for rats exposed to EDB vapor: 6 minutes at 3000 ppm (23,040 mg/m^3); 30 minutes at 400 ppm (3072 mg/m^3); and 2 hours at 200 ppm (1536 mg/m^3). Guinea pigs survived 400 ppm for 2 hours and 200 ppm for 7 hours. The maximum exposures without adverse effects in female rats were 800 ppm (6144 mg/m^3) for 6 minutes; 100 ppm (768 mg/m^3) for 2.5 hours; and 50 ppm (384 mg/m^3) for 7 hours. Pathological changes seen following acute exposures were congestion, edema, hemorrhage, and inflammation of the lungs; cloudy swelling, central lobular fatty degeneration, and necrosis of the liver; and slight interstitial congestion and edema of the kidneys with cloudy swelling of the tubular epithelium in some cases.

Rats were exposed in a fumigation chamber to 1040 ppm (7987 mg/m^3) EDB until death occurred. The lethal exposure times ranged from 5 to 165 minutes. Clinical signs of toxicity were reddened nasal mucous membranes, nosebleed, excessive salivation, anorexia, weight loss, and weakness (Akamine, 1952).

3.2.2. Subchronic Toxicity
3.2.2.1. Human

Information on the subchronic toxicity of EDB in humans following inhalation exposure was not available.

3.2.2.2. Animal

Groups of F344 rats and $B6C3F_1$ mice of both sexes were exposed to 3, 15, or 75 ppm EDB (23, 115, or 576 mg/m^3), 6 hours/day, 5 days/week for 13 weeks. Nasal cavity lesions such as cytomegaly, focal hyperplasia, squamous metaplasia, and loss of cilia were observed at 75 ppm in both species, but were absent at 3 and 15 ppm and in controls. No lesions were observed in other tissues (Reznik et al, 1980).

Nitschke et al. (1981) exposed male and female rats to 3, 10, or 40 ppm EDB (23, 77, or 307 mg/m^3), 6 hours/day, 5 days/week, with scheduled sacrifices after 1, 6, and 13 weeks of exposure and after a 88-day observation period following exposure. No adverse effects were noted at 3 ppm. At 10 ppm, slight epithelial hyperplasia in the nasal turbinates was seen during the exposure periods but not after recovery. The highest concentration produced decreased weight gain, increased liver and kidney weights, and hyperplasia and squamous metaplasia of the respiratory epithelium of nasal turbinates. Recovery from nasal lesions occurred during the observation period.

Rowe et al. (1952) exposed rats, guinea pigs, rabbits, and monkeys to 50 ppm (384 mg/m^3) EDB, 7 hours/day, 5 days/week for 70-91 days. High mortality attributed to respiratory tract infections occurred in male and female rats. Also seen in rats were increased liver and kidney weights (both sexes), increased lung weights (males), and decreased spleen weights (females). Decreased weight gain, slight fatty degeneration of the liver, and renal tubular epithelium degeneration were observed in guinea pigs. Slightly increased liver weights were the only effects seen in rabbits and monkeys.

3.2.3. Chronic Toxicity
3.2.3.1. Human

Ott et al. (1980) reported results of an epidemiological study of 161 male workers exposed to EDB in two manufacturing plants in Texas and Michigan. Concentrations in one plant ranged from 1 to 10 ppm (8-77 mg/m^3) in 1950 and from 19 to 31 ppm (146-238 mg/m^3, area samples) and up to 13 ppm (100 mg/m^3, drum filling) in 1952. Twenty years later, concentrations of 2 and 3.5 ppm (15 and 27 mg/m^3) were recorded; three episodes of exposure to concentrations between 100 and 200 ppm (768 and 1536 mg/m^3) were reported. No statistically significant increase in deaths due to respiratory disease was observed.

In another epidemiological study, the mortality of small groups of workers exposed to EDB in two manufacturing plants in England was evaluated. A comparison of mortality rates was done by grouping person-years of follow-up into four ranges over the 23-year study period. No increase in mortality from any cause was identified in EDB workers (Turner and Barry, 1979).

3.2.3.2. Animal

Nonneoplastic effects were reported in a carcinogenicity study conducted by NTP (1982). Groups of F344 rats and $B6C3F_1$ mice were exposed to 10 or 40 ppm EDB (77 or 307 mg/m^3), 6 hours/day, 5 days/week for 88-91 weeks (rats) or 78-103 weeks (mice) (NTP, 1982). The body weights of rats and mice (both sexes) exposed to 40 ppm were lower than those of untreated controls throughout the study. Rats developed nasal cavity hyperplasia and toxic nephropathy at 10 and 40 ppm. Mice developed nasal cavity inflammation and epithelial hyperplasia of the alveoli and bronchial tract, especially at the high concentration.

Rowe et al. (1952) exposed rats, guinea pigs, rabbits, and monkeys to 25 ppm (192 mg/m^3) EDB, 7 hours/day, 5 days/week for 213-220 days. No treatment-related effects were observed in any species.

Disulfiram (a drug used in the treatment of alcoholism) potentiates the toxic effects of EDB in experimental animals (see also Section 4.2.2). Wong et al. (1982) exposed Sprague-Dawley rats of both sexes by inhalation to 20 ppm EDB (157 mg/m^3) , 7 hours/day, 5 days/week for 18 months alone or with simultaneous exposure to 0.05% of disulfiram in the diet. Exposure to EDB caused splenic atrophy in males. Both sexes of rats exposed to EDB and fed the disulfiram diet had significantly decreased

erythrocyte counts, hematocrit, and hemoglobin values as well as splenic atrophy compared with rats exposed to EDB alone.

3.2.4. Developmental and Reproductive Toxicity

3.2.4.1. Human

A retrospective evaluation of the effects of EDB on the reproductive performance of chemical plant workers was conducted by Wong et al. (1978). Exposure of workers ranged form 0.5-5 ppm (4-38 mg/m^3) at plants A and B, <5 ppm (time-weighted average, TWA) at plant C, and 0.1-4 ppm (0.8-31 mg/m^3) at plant D. A total of 297 couples were included in the assessment (single men were excluded). Definite data regarding exposure durations were not provided. When all four plants were considered together, no significant anti-fertility effects (observed/expected births) could be attributed to EDB exposure. The observed/expected births ratio was significantly lower at plant D, but individual exposure data were not available.

Ter Haar (1980) evaluated the relationship between sperm count and EDB exposure in workers employed at a production plant for antiknock compounds in Arkansas. In the low-exposure group (<0.5 ppm EDB in the air), 20% of individuals had sperm counts below 40 million, while 42% in the high-exposure group (between 0.5 and 5 ppm) had sperm counts below 40 million.

A marked reduction in sperm count was reported in a small group of agricultural workers exposed to EDB in Molokai, Hawaii. Twenty three percent of the agricultural workers had low sperm counts (counts below 20 million/mL) compared with 14% of a reference group (Takashi et al., 1981). Ratcliffe et al. (1987) (see also Schrader et al., 1988) examined semen quality of 46 papaya workers exposed to EDB for an average duration of 5 years. These individuals worked in areas where fumigated fruit is sorted and packed, the areas usually being adjacent to fumigation chambers which were frequently opened to the work area. The 8-hour time-weighted-average (TWA) concentration was 88 ppb (0.7 mg/m^3) with peak exposures reaching 262 ppb (2 mg/m^3). A non-exposed control group consisted of workers from a nearby sugar refinery. Statistically significant decreases of sperm counts/ejaculate and percentage of viable and motile sperm, and significant increases of sperm with morphological abnormalities were detected in the exposed group.

3.2.4.2. Animal

Pregnant CD rats and CD-1 mice were exposed by inhalation to EDB at concentrations of 20, 38, or 80 ppm (154, 292, or 614 mg/m^3), 23 hours/day on gestational days 6 through 16 (Short et al., 1978). In rats, reduced food intake was observed in all exposed groups, with reduced body weight gains at $38 ppm. Increased mortality (50%) and a significant reduction in the viability of embryos and fetuses occurred at 80 ppm. Skeletal anomalies (incomplete ossification) were seen at concentrations as low as 20 ppm. Some soft tissue abnormalities were seen in fetuses of exposed rats but were not statistically significant. All exposed groups of mice had reduced body weight gains with reduced food consumption. All mice exposed to 80 ppm died, with mortality occurring also at 38 ppm. Fetotoxic effects consisted of significantly increased resorptions and reduced fetal body weight.

Male Sprague-Dawley rats exposed by inhalation to EDB at concentrations up to 89 ppm (684 mg/m^3) for 10 weeks developed atrophy of the testis, epididymis, prostrate, and seminal vesicles. None of the rats from the 89 ppm exposure group were able to impregnate female rats during a 2-week mating period following termination of exposure. It is uncertain whether the reproductive effects were due to EDB exposure or to malnutrition (Short et al., 1979). Exposure of F344 rats to 10 or 40 ppm EDB (77 or 307 mg/m^3), 6 hours/day, 5 days/week for 2 years produced testicular degeneration and atrophy in males (NTP, 1982). Rats, guinea pigs, rabbits, and monkeys were exposed to 50 ppm (384 mg/m^3) EDB, 7 hours/day, 5 days/week for 70-91 days. Decreased testicular weights were observed in rats but not in the other species tested (Rowe et al., 1952).

3.2.5. Reference Concentration
3.2.5.1. Subchronic

INHALATION RfC: 2E-3 mg/m^3 (U.S. EPA, 1995)
LOAEL: 88 ppb
UNCERTAINTY FACTOR: 100

PRINCIPAL STUDIES: Ratcliffe et al., 1987; Schrader et al., 1988
COMMENTS: The chronic RfC was modified to estimate the subchronic RfC.

3.1.5.2. Chronic

INHALATION RfC: 2E-4 mg/m^3 (U.S. EPA, 1995)
LOAEL: 88 ppb
UNCERTAINTY FACTOR: 1000

PRINCIPAL STUDIES: Ratcliffe et al., 1987; Schrader et al., 1988

COMMENTS: The chronic RfC is based on sperm effects in humans intermittently exposed by inhalation to EDB. The RfC is under review and may be subject to change (U.S. EPA, 1995).

3.3. OTHER ROUTES OF EXPOSURE
3.3.1. Acute Toxicity
3.3.1.1. Humans

Two workers died after entering a pesticide storage tank that contained residues of EDB. The primary route of exposure was dermal, but inhalation was also likely; the exposure times ranged from 20 to 45 minutes. Both men collapsed shortly after entering the storage area and died 12 and 64 hours later. Toxicological findings included metabolic acidosis, central nervous system (CNS) depression, and liver and kidney damage (Letz et al., 1984).

Serious skin injury can occur from clothing (particularly shoes) wet with EDB. When the chemical was accidentally spilled into shoes, prolonged contact of the skin with EDB resulted in reddening, blistering, and burning pain. In addition to leather, EDB can penetrate several types of protective clothing including neoprene rubber and plastic gloves (Torkelson, 1994).

3.3.2.2. Animals

The intraperitoneal LD_{50} for mice is 220 mg/kg and the dermal LD_{50} for rats and rabbits is 300 mg/kg (RTECS, 1996). Lethal amounts of topically applied EDB (undiluted or 10% solution in butylcarbitol acetate) are rapidly absorbed through the intact skin (Rowe et al., 1952). For a contact period of 24 hours, a dermal dose of 0.21 g/kg was survived by 14/15 rabbits; 1.1 g/kg killed 5/5 rabbits. A 1% solution of EDB in butylcarbitol acetate applied 10 times in 14 days to rabbits' ears caused slight irritation. The same repeated application, when bandaged to the shaved abdomen produced erythema and edema, progressing to sloughing of skin layers (Rowe et al., 1952).

Applied to the eyes of rabbits, undiluted EDB caused pain and conjunctival irritation that cleared within 48 hours. Also observed was a slight necrosis of the cornea; healing was prompt and complete (Rowe et al., 1952).

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of EDB in humans or animals by other routes of exposure was not available.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of EDB in humans or animals by other routes of exposure was not available.

3.3.4. Developmental and Reproductive Toxicity

3.3.4.1. Human

Information on the developmental and reproductive toxicity of in humans by other routes of exposure was not available.

3.3.4.2. Animal

Male rats were administered 5 daily doses of 5 mg EDB by intraperitoneal injection once weekly for 10 weeks prior to mating. Infertility was observed in the 4th week of mating and returned to normal in the following weeks, suggesting spermatid damage (Edwards et al., 1970).

3.4. TARGET ORGANS/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target Organs

1. Reproduction: Oral administration of EDB reduced sperm counts and motility and increased production of abnormal sperm in bulls. It produced testicular degeneration in mice and affected the egg-laying capacity in hens.

2. Gastrointestinal tract: Chronic exposure to EDB produced hyperkeratosis of the forestomach epithelium in animals. In humans, acute exposures caused erosion of the mouth, pharynx, and gastric mucosa.

3.4.1.2. Other Target Organs

1. Liver: EDB was weakly hepatotoxic in animals following chronic oral exposure.However, acute exposures produced severe liver necrosis in humans.

2. Kidneys: Renal lesions were described in humans acutely exposed to EDB.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target Organs

1. Nasal cavity: Nasal lesions developed in rats and mice following prolonged inhalation exposure.

2. Reproduction and Development: Decreased sperm counts have been reported in occupationally exposed individuals. EDB has induced testicular degeneration and atrophy and developmental effects (increased resorptions, reduced survival of fetuses, skeletal anomalies) in rodents at maternally toxic doses.

3. Kidneys: Increased kidney weights and nephropathy were observed in rodents following prolonged inhalation exposure.

4. Liver: Increased liver weights were observed in rodents following prolonged inhalation exposure.

3.4.2.2. Other Target Organs

Spleen: Chronic exposure has produced splenic atrophy in rats.

3.4.3. Other Routes of Exposure
3.4.3.1. Primary Target Organs

1. Skin: Contact of the skin with EDB has resulted in reddening, blistering, and burning pain.

2. Reproduction: Intraperitoneal injections administered before mating caused infertility in rats.

3.4.3.2. Other Target Organs

No other target organs by other routes of exposure were identified.

4. CARCINOGENICITY
4.1. ORAL EXPOSURES
4.1.1. Human

Information on the carcinogenicity of EDB in humans following oral exposure was not available.

4.1.2. Animal

In a bioassay by NCI (1978), male and female Osborne-Mendel rats were treated by gavage with EDB in corn oil 5 times/week at TWA doses of 38 or 41 mg/kg/day (males) and 37 or 39 mg/kg/day (females). High treatment-related mortality prompted alterations in the dosing regimen, resulting in similar TWA doses for the low- and high-dose groups and an early termination of the study (male rats were terminated after 49 weeks and female rats after 61 weeks of treatment.) $B6C3F_1$ mice received TWA doses of 62 or 105 mg/kg/day, 5 days/week for 53 weeks. Significantly increased incidences of squamous cell carcinomas of the forestomach (both species, both sexes), hepatocellular carcinomas and neoplastic nodules of the liver (female rats), hemangiosarcomas of the circulatory system (male rats), and alveolar/bronchiolar adenomas (mice, both sexes) were observed. Squamous cell carcinomas of the forestomach in the rats appeared as early as 12-15 weeks after the start of the treatment, and occurred in 97-100% of the high-dose males and the low- and high-dose females that survived beyond 15 weeks of treatment. In both dose groups, forestomach carcinomas developed in 78-92% of the male mice that survived 26 weeks and in 76-100% of the female mice that survived 14-18 weeks. No tumors were observed in control rats or mice.

Van Duuren et al. conducted two drinking water studies with $B6C3F_1$ mice (Van Duuren et al., 1985, 1986). In the first study, administration of 116 mg/kg/day (males) or 103 mg/kg/day (females) in drinking water for 15-17 months induced squamous cell tumors (primarily carcinomas) of the forestomach in both sexes. Because of high mortality, the animals were sacrificed before the planned termination of the study. In the second study, mice were administered a lower dose (50 mg/kg/day). Both sexes of mice had significantly increased incidences of squamous cell tumors of the forestomach (squamous cell carcinomas in males; papillomas or carcinomas in females). Male mice also had a significantly increased incidence of papillomas or carcinomas of the esophagus.

4.2. INHALATION EXPOSURES
4.2.1. Human

Cancer mortality was studied in 161 male employees exposed to EDB in two manufacturing plants in Texas and Michigan (for exposure details, see Section 3.2.3.1). Neither total deaths nor total malignancies were found to exceed the control rate (Ott et al., 1980).

Turner and Barry (1979) evaluated the mortality of workers exposed to EDB in two manufacturing plants in Great Britain. The manufacturing operation involved the extraction of bromine from sea water and its subsequent reaction with ethylene to form EDB. Although the size of the group was too small to analyze mortality rates on a year-by-year basis, a comparison was done by grouping person-years of follow-up into four age ranges over the period of the study (23 years). No increase in mortality from any cause, including cancer, was observed in the EDB workers.

4.2.2. Animal

Fischer 344 rats and B6C3F$_1$ mice of both sexes were exposed to EDB vapors at concentrations 10 or 40 ppm (77 or 307 mg/m^3), 6 hours/day, 5 days/week for life (NTP, 1982). Throughout the study, the body weights of rats and mice sex exposed to 40 ppm were lower compared to controls. Survival time of male and female rats (40 ppm) and female mice (10 and 40 ppm) was shorter than those of controls. The incidence of nasal cavity carcinomas and adenocarcinomas was significantly increased in male and female rats (10 and 40 ppm) and in male and female mice (40 ppm). Exposed rats also had increased incidences of splenic hemangiosarcomas (both sexes); mesotheliomas of the tunica vaginalis (males); pulmonary alveolar/bronchiolar carcinomas (females); and fibroadenomas of the mammary gland (females). Male and female mice had significantly increased incidences of alveolar/bronchiolar carcinomas and adenomas, and adenomatous polyps in tracheal, bronchial, and bronchiolar lumens. Female mice also developed hemangiosarcomas of the abdominal retriperitoneum (ovaries, uterus, kidneys, and adrenals); subcutaneous fibrosarcomas; and mammary adenocarcinomas.

In a chronic inhalation study of experimental design identical to the NTP (1982) study using B6C3F$_1$ mice only, Stinson et al. (1981) reported an increased incidence of nasal cavity carcinomas in female mice exposed to 40 ppm EDB (307 mg/m^3). Both sexes had dose-related epithelial hyperplastic lesions of the nasal cavity. Histological and pathological examinations were conducted only on the nasal cavity.

Disulfiram potentiates the carcinogenic effects of EDB in experimental animals. Wong et al. (1982) exposed Sprague-Dawley rats of both sexes by inhalation to 0 or 20 ppm EDB (154 mg/m^3), 7 hours/day, 5 days/week for 18 months alone or with simultaneous exposure to 0.05% disulfiram in the diet. Rats exposed to EDB alone had significantly increased incidences of splenic hemangiosarcomas (both sexes), subcutaneous mesenchymal tumors (males), and mammary gland tumors (females). In both sexes of rats, the combination of EDB and disulfiram resulted in significantly higher incidences of hepatocellular tumors; splenic hemangiosarcomas, kidney adenomas and carcinomas, thyroid follicular epithelial adenoma; and hemangioma of the omentum or mesentery. Female rats had an increased incidence of mammary tumors. Histological examination excluded the nasal cavity.

4.3. OTHER ROUTES OF EXPOSURE

4.3.1. Human

Information on the carcinogenicity of EDB in humans by other routes of exposure was not available.

4.3.2. Animal

Dermal application of EDB, three times weekly for 440-594 days, to Ha:ICR Swiss mice induced significantly increased incidences of skin papillomas at 50 mg and lung papillomas at 25 and 50 mg compared to controls. However, a single dermal application of 75 mg EDB followed by three weekly treatments with phorbol myristate acetate did not result in an increased papilloma incidence (Van Duuren et al., 1979).

4.4. EPA WEIGHT-OF-EVIDENCE

Classification -- Group B2, probable human carcinogen (U.S. EPA, 1996, 1995).
Basis: Increased incidences of a variety of tumors in rats and mice in both sexes by three routes of administration at both the site of application and at distant sites. The chemical is mutagenic in various *in vitro* and *in vivo* assays and is structurally similar to dibromochloropropane (DBCP) and ethylene dichloride (EDC), both classified as probable human carcinogens.

4.5. CARCINOGENICITY SLOPE FACTORS

4.5.1. Oral

SLOPE FACTOR: 8.5 (mg/kg/day)$^{-1}$ (U.S. EPA, 1996)
UNIT RISK: 2.5E-3 (µg/L)$^{-1}$ (U.S. EPA, 1996)
PRINCIPAL STUDY: NCI, 1978

COMMENT: The slope factor was calculated using a model that permits consideration of variable lifetime exposure. Conversions from gavage to oral/diet were made assuming that the relative potency of ingestion exposure compared to gavage exposure is the same for EDB and DBCP. DCPB is chemically similar to EDB, has been assayed in both ingestion and gavage studies in male rats, and caused the same types of tumors as EDB when administered by gavage.

4.5.2. Inhalation

SLOPE FACTOR: 7.6E-1 $(mg/kg/day)^{-1}$ (U.S. EPA, 1995)
UNIT RISK: 2.2E-4 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1996)
PRINCIPAL STUDY: NTP, 1982

COMMENT: The slope factor and unit risk are based on benign and malignant nasal cavity tumors observed in a chronic inhalation study with rats.

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