

## VI. DEVELOPMENT OF STANDARD

### Basis for Previous Standards

In 1953, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted a threshold limit value (TLV) of 25 ppm as an 8-hour TWA concentration for 1,2-dibromoethane (ethylene dibromide) [106]. No specific basis for this TLV has been found. In 1954, the ACGIH [107] changed the name to ethylene dibromide in the official TLV list, and, in 1956, they added the value of 190 mg/cu m to the official entry [108]. In 1962, the ACGIH [109] restored 1,2-dibromoethane as the principal designation of the compound and reported in the Documentation of the Threshold Limit Values of Substances in Workroom Air that the TLV of 25 ppm as a TWA concentration was based on the report of Rowe et al [33]. Rowe et al [33] reported that ethylene dibromide was readily absorbed through the intact skin of rabbits and from the gastrointestinal tract of rats, mice, guinea pigs, chickens, and rabbits. Ethylene dibromide vapor caused CNS depression, pulmonary irritation, and liver and kidney damage in rats and guinea pigs after single exposures. Rats, guinea pigs, monkeys, and rabbits tolerated repeated exposures of ethylene dibromide vapor at 25 ppm for 7 hours/day, 5 days/week, for about 6 months without adverse effects, but these species did not tolerate well a similar exposure at 50 ppm.

In 1965, the ACGIH [110] recommended that special emphasis be given to the potential for skin absorption of 1,2-dibromoethane by adding the designation "skin" after the name in the TLV list. Such a notation refers to the potential contribution to overall exposure by the dermal route, including mucous membranes and eyes, either by airborne, or more particularly, by direct contact with ethylene dibromide. This designation

was intended to indicate that measures for the prevention of absorption from skin and mucous membranes were necessary if the TLV was to be successful in limiting occupational exposure to a safe level. In 1965, the ACGIH [110] also recommended that the TLV of 25 ppm as a TWA concentration for ethylene dibromide be tentatively changed to a ceiling limit of 25 ppm. The basis [111] for this limit was primarily the report by Rowe et al [33], discussed previously, and the paper by Lucas [28]. Lucas [28] observed that single 10- to 12-minute exposures of rabbits to a concentration of ethylene dibromide vapor sufficient to produce anesthesia resulted in rapid breathing, phonation, and death within 15-18 hours. The shift of the TLV from a TWA value to a ceiling limit was made final in 1967.

In 1971, the ACGIH [112] recommended changing the ceiling limit of 25 ppm to an 8-hour TWA concentration of 20 ppm (145 mg/cu m). The 1971 Documentation of the Threshold Limit Values for Substances in Workroom Air [113] cited several studies with no particular emphasis on how the limit was set. These reports included Rowe et al [33], Lucas [28], Kochmann [23], Olmstead [25], Rowe et al [38], and McCollister et al [37], which are discussed in Chapter III. Presumably, the study by Rowe et al [33] was the principal basis on which the new limit was set. The proposed value of 20 ppm as a TWA concentration was adopted in 1973 [114]. The basis for this change as stated in the 1974 supplement of the 1971 Documentation [113], did not differ from that stated in 1971.

In 1976, the ACGIH [115] added to the TWA value a tentative short-term exposure limit (STEL) of 30 ppm (220 mg/cu m), which is defined as a maximal concentration to which workers can be exposed for a period up to 15 minutes continuously. No more than 4 such excursions are permitted each day, with at least 60 minutes between successive exposure periods. Also,

the daily TLV-TWA is not to be exceeded.

Florida, Mississippi, Pennsylvania, and South Carolina have adopted a TWA concentration of 25 ppm (190 mg/cu m) as their environmental limit for ethylene dibromide [116].

In Finland, the German Democratic Republic, and Yugoslavia, the maximum allowable concentration (MAC) for the workplace environment is 190 mg/cu m (25 ppm) [116]. In the Rumanian Socialist Republic, 200 mg/cu m (approximately 26 ppm) of ethylene dibromide is the maximum concentration allowed in the occupational environment, whereas in Poland, the MAC allowed for ethylene dibromide is 100 mg/cu m (13 ppm) [116]. Although the USSR does not currently recommend a standard for ethylene dibromide, the US recommendation of 145 mg/cu m (20 ppm) is stated to be inadmissibly high. The 1976 edition of the Handbook for Chemists, Engineers and Physicians [117] states that, in all likelihood, the permissible concentration should be on the same order as the Russian MAC for dichloroethane (12.5 ppm) or lower [117]. No bases for these standards have been found.

The current federal standard (29 CFR 1910.1000) for occupational exposure to ethylene dibromide is 20 ppm as an 8-hour TWA limit, with an acceptable ceiling concentration of 30 ppm. A maximum peak above the acceptable ceiling concentration for an 8-hour work shift of 50 ppm not to exceed 5 minutes (Federal Register 40:103, May 28, 1975) is also permitted. This standard was adopted from the American National Standards Institute (ANSI) recommendation Z37.31-1970 [3], which was based on the reports of Rowe et al [33] and Olmstead [25], and the summary presentation by Irish [4], which includes synopses of several other reports [23,24,27,33] discussed in Chapter III.

## Basis for the Recommended Standard

### (a) Environmental (Workplace Air)

Employees exposed to ethylene dibromide vapor may suffer deleterious effects which may be delayed in their onset. Single short-term exposures to sublethal concentrations have resulted in conjunctival irritation, glandular swelling, and a generally poor condition, while repeated exposures to sublethal concentrations have resulted in conjunctivitis, pharyngeal and bronchial irritation, anorexia, headaches, and depression [23]. Exposure to a lethal inhaled dose of ethylene dibromide vapor derived from some unknown portion of an estimated 70 g of the liquid applied to an anesthesia mask produced nervousness, vomiting, diarrhea, abdominal pain, upper respiratory irritation, degeneration of the parenchymal tissue in the heart, liver, and kidneys, and hemorrhaging into the trachea, blood vessels, and along the sternum, culminating in death about 44 hours after the exposure [22].

Ethylene dibromide in humans produces blistering when the liquid is allowed to remain in contact with the skin for more than 10 minutes and can cause death when ingested. Volunteers subjected to dermal contact with ethylene dibromide for up to 10 minutes, developed burning pain and reddening of the skin; blistering occurred after prolonged contact [24]. Repeated dermal exposure caused a skin sensitization to ethylene dibromide in one of the volunteers. Ingestion of about 4.5 ml (140 mg/kg) of ethylene dibromide caused the death of a 43-year-old woman [25]. Prior to death 54 hours after ingestion, she developed diarrhea, vomiting, anuria, tachypnea, nervous agitation, abdominal pain, systolic heart murmurs, sinus tachycardia, and an arrhythmic, sporadic pulse. Autopsy results indicated edema and congestion of the lungs, intestinal mucosal erythema, massive

centrilobular liver necrosis, and tubular epithelial damage in the kidneys.

Animal experiments confirm and extend the clinical observations of the effects reported in humans that have been exposed to ethylene dibromide. A dog exposed to 1 ml of vaporized ethylene dibromide (a calculated concentration of about 2,830 ppm or 21,790 mg/cu m) for 1 hour showed signs of ocular irritation, including corneal opacity, that developed into purulent conjunctivitis in both eyes and ulceration of one cornea [31]. Conjunctivitis also developed in cats exposed to 100 ppm (770 mg/cu m) of ethylene dibromide for 30 minutes/day for approximately 10 days [23], and conjunctival irritation was noted in rabbits after instillation of undiluted, 10%, or 1% solutions of ethylene dibromide [33]. The irritation subsided within 2-12 days in the rabbits without causing corneal scarring. Marked hyperemia of the cutaneous blood vessels surrounding the application site was found after 0.25, 0.50, or 1.0 ml (0.55, 1.1, or 2.2 g) of ethylene dibromide was applied to the abdomen of rats [27]. Rabbits responded similarly when undiluted or 10% solutions of ethylene dibromide were applied to the abdomen [33]. Application of 210 mg/kg of the undiluted chemical caused marked erythema, edema, and necrosis of the skin.

Respiratory tract irritation caused by ethylene dibromide vapor has been seen in guinea pigs after single exposures at 2,000 ppm (15,400 mg/cu m) for 150 minutes [27], and for cats after exposures as low as 100 ppm (770 mg/cu m) for 30 minutes [23]. A strong reddening of the nasal mucosa was observed after three 30-minute exposures at 100 ppm (770 mg/cu m) [23]. A dog exposed to 5 ml (11.0 g) of vaporized ethylene dibromide for 1 hour in a 100-liter chamber developed severe bleeding in the right lung, and another dog exposed to 1 ml (2.2 g) for 1 hour had severe hyperemia and bronchopneumonic foci in both lungs [31]. The lungs of rats

exposed to ethylene dibromide at concentrations between 100 and 10,000 ppm (770 and 77,000 mg/cu m) for 0.02-16.0 hours were congested, edematous, hemorrhagic, and inflamed [33].

Repeated exposure of cats to concentrations of ethylene dibromide of 100 ppm (770 mg/cu m) for 30 minutes daily for an average of 10 days caused discoloration and partial dysfunction of the lungs [23]. Pulmonary infection, probably a secondary result of the irritation of the lungs by ethylene dibromide, was responsible for a 50% mortality in male rats and guinea pigs and a 25% mortality in female guinea pigs exposed repeatedly to 25 ppm (192.5 mg/cu m) of ethylene dibromide for 7 hours/day, 5 days/week, for about 6 months [33]. Similar mortality was not observed in the control group exposed in a chamber ventilated with clean air, although high mortality was observed in the control animals simply maintained in the colony.

Other systemic damage also occurred in animals after single and repeated exposures to ethylene dibromide vapor. Guinea pigs exposed at concentrations of ethylene dibromide of 2,000 ppm (15,400 mg/cu m) for 150 minutes developed a pronounced granular degeneration of the parenchymal tissue of the kidneys and a slight degeneration of the parenchymal tissue of the liver, spleen, and heart [27]. Rats exposed at concentrations between 100 and 10,000 ppm (770 and 77,000 mg/cu m) of ethylene dibromide for 0.02-16.0 hours developed cloudy swelling, centrilobular fatty degeneration, and necrosis of the liver, cloudy swelling and a slight interstitial congestion and edema of the kidneys, and CNS depression at the higher concentrations [33].

Repeated inhalation exposures of rats for 7 days and rabbits for 3-4 days at 100 ppm (770 mg/cu m) of ethylene dibromide for 7 hours/day

produced slight congestion of the spleens of rats, cloudy swelling and a slight leukocytic infiltration in the livers of rats, and widespread central fatty degeneration and some necrosis in the livers of rabbits [33]. Exposure of guinea pigs and monkeys at 50 ppm (285 mg/cu m) of ethylene dibromide for 7 hours/day, 5 days/week, for 70-80 days caused only slight central fatty degeneration of the liver [33]. Cats exposed at 100 ppm (770 mg/cu m) of ethylene dibromide for 30 minutes/day for about 10 days had enlarged spleens. Death resulted from circulatory system damage to the heart and vessels [23].

CNS effects, such as agitation, restlessness, body tremors, or unconsciousness, are caused by exposure to ethylene dibromide [23,29-31], but they have not been sufficiently described to permit an adequate evaluation or quantitation of their relevance or validity.

The information provided by the few reports on humans [22-25] and such experimental animal data as those given in the following references [23,27,31,33] indicates that many effects produced by ethylene dibromide on humans and animals are similar and differ only in magnitude. Respiratory tract irritation, damage to the liver, kidneys, spleen, and lungs, irritation of the skin and eyes, and gastrointestinal disturbances are the predominant effects of ethylene dibromide exposure. Since systemic effects may occur from ingestion, inhalation, or dermal contact with ethylene dibromide, NIOSH recommends that work practices be used to minimize employee exposure to ethylene dibromide liquid or vapor through inhalation, body or eye contact, or ingestion.

Mammalian studies indicate that reproductive abnormalities, including antifertility [9] and spermatozoic anomalies [41-43], occur from exposure to ethylene dibromide. One report [9] indicated that five ip injections of

10 mg/kg given to male rats produced a decrease in fertility only during the 3rd and 4th weeks after injection. Since spermatids require about 3-4 weeks to mature into spermatozoa in the rat, the evidence indicates that ethylene dibromide affects the development of the spermatids that were present at the time of injection. This is further supported by the return of normal fertility 5 weeks after the injection. Three studies with bulls [41-43] that received an average daily dose of 2 mg/kg of ethylene dibromide for various periods during their development indicated that the abnormalities expressed in their reproductive systems were the result of the action of ethylene dibromide on the maturation step in the spermatogenic cycle and not a direct action of ethylene dibromide on the germinal tissue. Discontinuance of administration of ethylene dibromide resulted in reversal of the impairment, and the bulls produced normal semen and spermatozoa until ethylene dibromide administration was begun again in one of the studies [41]. In another experiment [42], production of abnormal spermatozoa occurred with a dose as small as 4 mg/kg given on alternate days for seven doses. These spermatozoic abnormalities would greatly reduce the fertility, even if they did not cause total sterility. Although these effects were from the ingestion of ethylene dibromide and not from inhalation or dermal contact, they indicate that a hazard, including decreased fertility and even temporary sterility, may result from inhalation or percutaneous absorption of ethylene dibromide.

One study, reported by several authors [56-59], was conducted to determine the carcinogenic properties of ethylene dibromide. Rats and mice given daily oral doses by gavage of ethylene dibromide at 40 and 60 mg/kg, respectively, for 52-64 weeks developed squamous cell carcinomas in the stomach. These carcinomas invaded locally and metastasized throughout the



abdominal cavity. Male and female rats developed stomach carcinomas as early as 10 weeks after the start of administration of ethylene dibromide. The carcinomas became more prevalent as the daily doses of ethylene dibromide were continued, and the final percentage of male rats with tumors after administration of 40 mg/kg/day was 98% after termination of the experiment at 54 weeks. Male rats were more susceptible to tumorigenesis than female rats; 80% of all the males in the study developed tumors versus 38% of all the females. The concurrent control populations did not develop squamous cell carcinomas. More than 70% of all the mice were reported to have developed squamous cell carcinomas of the stomach by the termination of the experiment at 62 weeks. Since the numbers of tumors induced by nearly equivalent quantities of ethylene dibromide administered at different dose rates and on different schedules were substantially different, the experimental data are not consistent with a single-hit model of cancer induction for ethylene dibromide after administration by gastric tube in the rat. However, these data suggest that repeated ingestion of ethylene dibromide by humans may result in gastric carcinomas. At the present time, the induction of cancers by ethylene dibromide by other routes of exposure has not been demonstrated.

The mutagenic potential of ethylene dibromide is well established in both animal and plant systems. It induces mutations in vertebrate cell cultures [62], insects [6], bacteria [60,63,64], plants [66], and fungi [67,68].

One study with *Drosophila melanogaster* [6] showed that ethylene dibromide induced a significant number of recessive lethal mutations in three successive broods of offspring. The adult males fed 0.3 mM of ethylene dibromide for 3 days produced subsequent brood patterns indicative

of impaired spermatozoic maturation rather than of impaired formation. Studies with mouse lymphoma cells [62] indicated that a dose-related effect, typical of those of other alkylating agents tested, existed over the range of 0.0-3.0 mM ethylene dibromide. The effect of the highest concentration was approximately equal to that of a dose of 600 R of X-irradiation.

A study in a host-mediated assay system [60] with *Salmonella typhimurium* G46 in mice suggested that ethylene dibromide was mutagenic at a dose of 500 mg/kg. A second part of this study [60] showed that an equivalent dose produced a positive mutagenic effect on *Salmonella typhimurium* G46 in vitro, indicating that ethylene dibromide did not require metabolic activation and was not deactivated by metabolism. Similar positive mutagenic results occurred in *Salmonella typhimurium* TA 1530 at 5  $\mu$ l (11.0 mg)/plate [63] or 10  $\mu$ M/plate [64] and in *Salmonella typhimurium* TA 1535 at 10  $\mu$ M/plate [64]. A linear relationship for mutation responses occurred over the range of 3.6-148.2 ppm (27.72-1,141.14 mg/cu m) in *Tradescantia* clone 4430 [66], exhibiting a well-defined dose response with single exposures to as little as 3.6 ppm (27.72 mg/cu m) of ethylene dibromide for 6 hours.

Several studies [5,6,64] suggest that the mechanism of mutagenic activity of ethylene dibromide is based on its ability to alkylate, or covalently bond to, DNA in the exposed cells. Ethylene dibromide is a bifunctional alkylating agent capable of introducing cross-links into biologic materials [6] by displacement of the two reactive bromine atoms by reacting with amine, sulfhydryl, carboxy or other electron-donating groups. Ethylene dibromide, or its metabolites, has interacted with DNA through covalent bonds to induce DNA repair synthesis in opossum lymphocyte cells

[5]. Another indication of ethylene dibromide's ability to alkylate DNA is that ethylene dibromide is mutagenic in *Salmonella typhimurium* TA 1530 and TA 1535, both transitional mutational systems [64]. These data [5,6,64] suggest strongly that the most plausible chemical basis for the mutagenic activity of ethylene dibromide in procaryotic and eucaryotic organisms is its alkylation of cellular constituents such as DNA. This broad biologic reactivity suggests that ethylene dibromide may be capable of increasing spontaneous mutation rates in humans. However, the quantitative aspects of this potential have not been determined. Since the process of induction of mutations is a stochastic, virtually irreversible process, any increased frequency of mutation in exposed populations would accumulate as a function of the total absorbed dose of ethylene dibromide. Therefore, an adequate assessment of the importance of the plant and submammalian animal data in extrapolating to the concentrations of airborne ethylene dibromide present in the workplace environment is difficult, but the widespread mutagenic activity of ethylene dibromide does give cause for concern about damage to the genetic mechanisms in employees working with it.

The teratogenic effects found in a rat and mouse study [69] involved brain and costal anomalies in the offspring of dams exposed to ethylene dibromide. Pregnant rats and mice were exposed at a concentration of about 32 ppm of ethylene dibromide for 23 hours/day on days 6-16 of gestation. Some of the effects were attributed to malnourishment, but the abnormalities in the ethylene dibromide-exposed rats and mice were significantly different, both qualitatively and quantitatively, from those in the nonexposed controls; some of these abnormalities did not appear in mice fed a restricted amount of the normal diet whereas others appeared in both the restricted and the control mice with about the same incidences.

These data suggest that ethylene dibromide causes fetal anomalies in mice and rats that are not caused by malnourishment alone. Since inhalation is one of the major routes of exposure for the employee, these data suggest also that the babies of female employees may be subject to increased risks of developmental defects if their mothers are exposed to ethylene dibromide in the workplace during the critical phases of pregnancy.

The total risk to the health of employees exposed to ethylene dibromide is the result of the compounded risks from carcinogenicity, mutagenicity, teratogenicity, sterility, and damage to the kidneys, liver, spleen, respiratory tract, central nervous system, circulatory system, skin, and eyes. Although no comprehensive epidemiologic studies have been conducted to assess adequately these risks in the industrial environment, evidence of their existence in experimental animal systems or in isolated human exposures to ethylene dibromide has been discussed above and in Chapter III. Experimentation conducted with animal models, as outlined above, generally supports the findings observed in the limited number of human exposures.

Concern for employee health requires that the probability of the occurrence of long-term effects of ethylene dibromide be minimized. The preliminary report available to NIOSH from a review of the mortality experience of 161 employees of one manufacturer [26,71] may indicate that employees exposed to unknown concentrations of ethylene dibromide from industrial processes operating under the current federal standard of 153 mg/cu m (20 ppm) are not suffering measurable long-term effects. The authors (26), while recognizing the limitations posed by the small study group and the variety of toxic agents to which the employees may have been exposed stated, however, that an indication of increased mortality due to

ethylene dibromide exposure may have existed in one of the plants. An individual exposed to 153 mg/cu m (20 ppm) of ethylene dibromide for 40-46 weeks/year with a calculated minute volume of about 10 liters/minute would inhale approximately 6,700 g during 40 years of occupational exposure, which is about 8.7 times the lifetime oral doses (10.8 and 11.2 g/kg) that induced stomach cancer in the rat. In addition, the extensive experimental evidence on the induction of adverse effects in lower species [5-7,9,33,41-43,56-60,62,66,69] and the formation of stable covalent bonds between ethylene dibromide and cellular constituents [7,11] indicate that the occupational exposure limit should be lowered to decrease the potential hazard to employees.

Because of the intrinsic, stochastic, and virtually irreversible character of the chemical reactions that initiate the carcinogenic and mutagenic processes, the risk of adverse effects is a function of the rate of absorption and the total absorbed dose. Consequently, this risk can be reduced to any value necessary to protect the employees by decreasing both the absorption rate (to prevent saturation of the enzymatic detoxification mechanisms) and the total lifetime dose (to reduce the probability of deleterious stochastic processes, such as carcinogenesis and mutagenesis, from occurring).

The unusual complexity of the dynamics of the cellular response mechanisms to ethylene dibromide intoxication is emphasized by the dose-rate effect relationship observed for induction of gastric neoplasms. Daily intragastric doses of 40 and 60 mg/kg induced tumors in rats and mice within 10 weeks [56], whereas daily 7-hour inhalation exposures of about 49 mg/kg did not result in the observation of tumors even after 30 weeks [33]. The data suggest that one of the major factors in the development of gastric

carcinomas is direct contact between the mucosal cells and ethylene dibromide, and that a major difference in tumor induction may exist between the two routes of exposure. However, the animals used in the inhalation study were not maintained until the end of their normal lifespan; therefore, a direct comparison between the final incidences of tumors initiated by the two routes of exposure cannot be made.

A plausible pharmacokinetic explanation for the observed differences exists. Since the rat's capacity to metabolize ethylene dibromide [50] exceeds the rate of absorption (at 25 ppm) by a factor of at least 100, the concentration of ethylene dibromide in tissues should be considerably less than that in the air, which is about 1.02  $\mu$ moles/liter at 25 ppm [33]. The concentration of ethylene dibromide in corn oil used in the intubation study ranged between 0.066 and 0.132 moles/liter. Consequently, the mucosal cells of the stomach may have been exposed for short periods to concentrations of ethylene dibromide up to 100,000 times that to which lung tissue would be exposed during inhalation exposures at 25 ppm (192.5 mg/cu m). The saturation of enzymatically catalyzed detoxification and repair mechanisms may occur in the stomach tissues, resulting in an amplification of the tissue damage, which otherwise may be minimal. These pharmacokinetic considerations are consistent with the experimental results of Rowe et al [33], where the product of the concentration and duration of exposure to produce 50% mortality among the exposed rats was found to be approximately constant for higher concentrations of ethylene dibromide but not for lower ones. The evidence indicates that tissue detoxication and repair mechanisms exist, but that they cannot negate completely the intrinsic capacity of ethylene dibromide to alkylate cellular constituents. Because of this, exposure to ethylene dibromide has potentials for the

induction of adverse effects by both local and systemic actions. Reducing the concentration of ethylene dibromide in the air should optimize the protection to the organism afforded by cellular detoxication and repair mechanisms, thus minimizing the accumulation of ethylene dibromide in tissues and decreasing the subsequent cellular damage to a negligible level.

In summary, the limited reports of effects on humans along with experimental animal data indicate that the adverse effects which have been observed from exposure to ethylene dibromide are similar and that differences are primarily ones of magnitude. Epidemiologic evidence of adverse effects in workers is confined to a single mortality study which was hampered by small cohort size, mixed exposures, and minimal findings which were not sufficient to adequately identify a worker problem. The findings are regarded as little more than preliminary observations; nevertheless, increased deaths from malignancies cannot be ruled out and seem to have been most apparent in employees having 6 or more years exposure in ethylene dibromide operations. Available animal data indicate reversible reproductive abnormalities manifested as abnormal development of spermatozoa in young bulls and decreased fertility in rats at a time which indicated interference with the normal development of spermatids into mature spermatozoa. Carcinomas of the stomach invading into the abdominal cavity have been produced in mice and rats administered ethylene dibromide by direct intubation into the stomach. Cancers resulting from ethylene dibromide administration have not been demonstrable by any other route of administration. A major factor in the development of gastric carcinoma in the rats and mice is considered to be the direct contact between mucosal cells and concentrated ethylene dibromide in a quantity which exceeded the ability of the tissues to handle the chemical. Mutagenic effects from

ethylene dibromide have been demonstrated in microbes, plants, insects, and mammalian cells in vitro, presumably due to its ability to alkylate, or covalently bond, to DNA in a cross-linking mechanism by virtue of its bifunctional structure. Although this potential has not been demonstrated in humans, the broad biologic activity of ethylene dibromide warrants concern about possible damage to genetic mechanisms in employees exposed to it. Teratogenic effects which seem to be due to maternal exposure to ethylene dibromide have been confined to brain and costal anomalies in fetal mice and rats, but malnourishment as a contributing factor cannot be discredited unequivocally.

Although it is not possible at this time to state categorically an exposure concentration at which ethylene dibromide may be regarded to be completely without risk, NIOSH considers that the recommended occupational exposure limit should be substantially lower than the current federal standard of 20 ppm as an 8-hour TWA limit, 30 ppm ceiling. The recommended occupational exposure limit for ethylene dibromide, at the least, should be reduced sufficiently to keep the total lifetime dose well below the cumulative doses shown to be hazardous in animal experiments. In considering the alkylating capability of ethylene dibromide and the potential adverse effects on the organism which may result, especially at the subcellular level, NIOSH recommends that the occupational exposure limit for ethylene dibromide be reduced to a ceiling concentration of 1.0 mg/cu m (0.13 ppm) for any 15-minute sampling period. This represents a reduction to one-two-hundred and thirtieth of the current federal ceiling limit for ethylene dibromide and is a level at which an employee would inhale a maximum of about 686 mg/kg of ethylene dibromide during a 40-year working lifetime, which is substantially below that total dose known to induce adverse effects in experimental animals. It is believed that so



long as care is taken to prevent entrance of any appreciable amount of ethylene dibromide into the digestive tract, adherence to this exposure limit will protect against acute adverse effects and will reduce the potential long-term effects to a negligible level. NIOSH concludes that reduction to a ceiling concentration of 1.0 mg/cu m (0.13 ppm) will protect employees from acute illness resulting from exposure to ethylene dibromide and will reduce markedly, and perhaps remove entirely, any hazard of adverse effects on health from long-term exposure to this chemical.

It is recognized that many employees work with solid or liquid forms of ethylene dibromide in situations where there may be contact with the substance, resulting in dermal, ocular, or systemic effects. Consequently, appropriate work practices, training, and other protective measures should be required regardless of concentrations of airborne ethylene dibromide. Therefore, occupational exposure to ethylene dibromide has been defined as work in an area where ethylene dibromide is manufactured, blended, stored, used, handled, or otherwise present. The action level is defined as one-half the recommended occupational exposure limit, thereby delineating those work situations which do not require the expenditure of resources for environmental monitoring and associated recordkeeping.

(b) Sampling and Analysis

The technology is currently available to sample and analyze ethylene dibromide at the recommended occupational exposure limit to allow institution of the proper engineering controls. As discussed in Chapter IV and presented in greater detail in Appendices I and II, a charcoal tube method is recommended for personal breathing zone sampling of airborne ethylene dibromide. Gas-liquid chromatography is recommended for analyzing the trapped ethylene dibromide.

(c) Medical Surveillance and Recordkeeping

Several human [22-25] and animal [23,27,31,33] studies reported that exposure to ethylene dibromide vapor or liquid produced skin, eye, or respiratory irritation, CNS disorders, systemic damage in the liver, kidneys, spleen, lungs, and heart, and death. Thus, a medical surveillance program should include preplacement and periodic medical examinations that give attention to the nervous system, skin, eyes, lungs, kidneys, spleen, liver, and circulatory system. Medical attention should be provided for employees accidentally exposed to ethylene dibromide. Because ethylene dibromide induces cancer and mutations in experimental animals, it is recommended that all medical and other pertinent records involving ethylene dibromide exposure be kept for 30 years after termination of employment. This will allow enough time for future detection of chronic sequelae which may be related to the employee's known occupational exposure. Because of the possibilities of impaired development of fetuses and of the induction of sterility in men, employees of reproductive age must be counseled to minimize exposure to ethylene dibromide.

(d) Personal Protective Equipment and Clothing

Dermal [24,33] and ocular [23,33] contact with liquid ethylene dibromide induces irritation of the skin and eyes in humans and animals. Therefore, care must be exercised to ensure adequate protection against contact with ethylene dibromide. Personal protective clothing, including ocular protective devices and impervious work clothes, should be available and worn where exposure to ethylene dibromide is likely. Work practices that prevent skin and eye contact must be followed. Showers and eyewash fountains must be available for immediate use if accidental contact occurs.

(e) Informing Employees of Hazards

A continuing education program is an important part of a preventive hygiene program for employees occupationally exposed to hazardous materials

such as ethylene dibromide. Properly trained persons should periodically apprise employees of possible sources of ethylene dibromide exposure, the adverse health effects associated with such exposure, the engineering and work practice controls in use and being planned to limit exposure, and the environmental and medical monitoring procedures used to check on control procedures and on the health status of employees. Personnel occupationally exposed to ethylene dibromide must be warned and advised of the adverse effects of accidental exposure and must be informed of the signs and symptoms of the disorders. Employees should be warned that the onset of these symptoms may be delayed. If skin or eye contact occurs, the affected areas should be immediately flushed with copious amounts of water and examined by a physician.

(f) Work Practices

Because ethylene dibromide can produce death from ingestion [25] and has been found to induce gastric cancers in experimental animals [56], it is recommended that food storage, handling, dispensing, and eating be prohibited in ethylene dibromide work areas regardless of the air concentrations. In addition, it is recommended that employees who work in an ethylene dibromide area thoroughly wash their hands before eating, smoking, or using toilet facilities.

Engineering controls must be used whenever possible to control concentrations of airborne ethylene dibromide within the recommended occupational exposure limit. Where ethylene dibromide is present, a closed system of control should be used. During the time required to install adequate controls and equipment, to make process changes, to perform routine maintenance operations, or to make emergency repairs, exposure to ethylene dibromide can be minimized by the use of respirators and protective clothing. However, respirators should not be used as a substitute for proper engineering controls for normal operations.