HEALTH EFFECTS OF ETHYLENE DIBROMIDE (EDB)

Prepared by

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April 15, 1985

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1. Executive Summary

The adverse health effects indicative of systemic toxicity of ethylene dibromide (EDB), and reproductive effects, occur at levels thousands of times higher than the general ambient levels in California urban environments. Therefore, the ambient levels found in these environments are not expected to result in any of these effects.

EDB, however, is a potent carcinogen in more than one animal species, and could thus be of concern at low levels in ambient air. When administered to animals, EDB caused malignancies both at the site of first contact (skin, forestomach, and nasal cavity), as well as at remote sites (circulatory system, lung, and pituitary, among others).

The one published epidemiological study of 161 workers failed to show a statistically significant increase in cancer rates, but staff of the California Department of Health Services (DHS) agrees with its authors that it can neither rule out nor establish EDB as a human carcinogen because of the small size of the population studied. DHS staff agrees with the International Agency for Research on Cancer (IARC) in considering that there is sufficient evidence in animals for carcinogenicity. DHS staff recommends that it be considered potentially carcinogenic in humans.

EDB and its metabolites are genotoxic. There is no evidence to suggest that the carcinogenicity of EDB would have a threshold (a level below which there would be no effect). There is not sufficient information

about human and animal metabolism of EDB to allow pharmacokinetic modeling in risk assessment.

The Federal Occupational Safety and Health Administration (OSHA) has recently discussed risk assessments on EDB based on animal bioassays. OSHA staff accepted Brown's risk assessment (Appendix A) in which the multistage model and the one-hit model were applied to combined nasal tumors and combined hemangiosarcomas occurring in rats in two inhalation bioassays carried out by the National Toxicology Program/National Cancer Institute (NTP/NCI) and the Midwest Research Institute/National Institute for Occupational Safety and Health (MRI/NIOSH).

DHS staff performed an independent risk assessment based on nasal malignancies (adenocarcinomas, carcinomas, and squamous cell carcinomas) in male rats and hemangiosarcomas in female mice in the NCI study. Table A shows the risk estimates for occupational exposure at 20 parts per million (ppm) and community exposure at 10 parts per trillion (ppt) using the probit model, the multistage model, and the Weibull-multistage model.

The risks estimated using these models are not grossly incompatible with the results from the one published epidemiological study. DHS recommends the use of an excess lifetime risk value between 1.02 and 5.53 per million for each 10 ppt of EDB exposure. (This recommendation is based on the maximum likelihood estimate [MLE] from the simple multistage model for hemangiosarcomas in female mice and on the 95% upper confidence limit [UCL] estimates from the Weibull-multistage model for nasal malignancies in male rats). The values represent the theoretical risks of cancer

accumulated over a 70-year lifetime with a continuous average daily exposure for all 70 years.

It should be noted that the range between the maximum likelihood estimate and the 95% upper confidence limit represents only the statistical uncertainty introduced by the typically small size of the animal studies of carcinogenic effect. Other perhaps more important uncertainties are introduced by the choice of scaling factor between humans and animals, the choice of extrapolation models, and the additive, synergistic, or antagonistic effects of other chemicals. It should be noted that synergism was demonstrated between EDB and disulfiram (Wong et al., 1982), a substance which interferes with EDB's metabolism. On the other hand, DNA repair mechanisms, detoxifying enzymes, and other factors might lower the risk below what has been calculated. These uncertainties are particularly to be noted in a case such as that of EDB where the ambient exposures are at the low parts per trillion level while the animal experiments occurred at exposure levels more than a million times higher.

A lifetime risk of 1.02-5.53 per million population from a 10 ppt exposure must be viewed in the context of the overall probability of developing cancer, which is on the order of 250,000 cases per million population (25%) over a 70-year lifetime.

Table A

Risk Assessment Estimates for EDB
Showing Number of Excess Cancer Cases
from Lifetime Exposure[1]

Species/Tumor	Model	UCL*/MLE**	20 ppm Occupational Exposure (PEL)***	10 ppt Community Exposure
Male Rats				
Nasal Malignancies	Weibull-Multistage	95% UCL	985/1000	5.53/million
		MLE	916/1000	2.85/million
	Multistage	95% UCL	708/1000	3.15/million
		MLE	627/1000	2.53/million
	Probit	95% UCL	721/1000	0§/million
		MLE	638/1000	0§/million
Female Mice				
Hemangiosarcomas	Weibull-Multistage	95% UCL	732/1000	3.23/million
		MLE	549/1000	2.03/million
	Multistage	95% UCL	406/1000	1.34/million
		MLE	328/1000	1.02/million
	Probit	95% UCL	438/1000	0§/million
		MLE	357/1000	0§/million

* UCL - Upper confidence limit
** MLE - Maximum likelihood estimate
***PEL - Permissible Exposure Limit (Proposed for revision by OSHA, 1983. See Appendix A.)
§= Predictions for probit model ranged from 0 - 10^{-31}

[1]Given that Section 39650 of the Health and Safety Code stipulates that DHS "shall utilize scientific criteria which are protective of public health consistent with current scientific data", DHS staff does not propose to routinely present the 95% lower confidence limit which has a 95% theoretical probability of being an underestimate under the assumptions of the model used. In reality, the true risk may be considerably below even the 95% lower confidence level but there is no scientific basis for locating where this is. For this reason we present the maximum likelihood and 95% upper confidence limit estimates and explain that these lifetime risk values represent a range of conservative estimates and are unlikely to be exceeded by the actual risk.

2. Introduction

This document provides a health assessment for exposure to ethylene dibromide (EDB) in ambient air. Due to the time limitations on preparing this document and the existence of a recent, excellent document by the Federal Occupational Safety and Health Administration (OSHA, 1983; Appendix A), frequent reference is made to that review. The Department of Health Services (DHS) staff has, however, carried out its own evaluation and assessments in the areas of pharmacokinetics, reproductive effects, cancer risk assessment, and the compatibility between risk assessment and epidemiological evidence. The reader can obtain the essential information about ambient exposure to airborne EDB by reviewing the DHS document. More detail can be found in the appendices, particularly Appendix A, the OSHA review.

3. Chemical Properties

Data on the physical and chemical properties of EDB have been summarized by OSHA and can be found in Appendix A, P.45957 under II (A), Chemical Identification.

4. Health Effects

4.1 Animal

The acute toxicity of EDB has been reviewed and summarized by OSHA as provided in Appendix A, P.45960 under III (A), Acute Toxicity.

EDB is very toxic when applied in single doses. The median lethal dose (LD_{50}) for EDB in several animal species ranges from 55 milligrams per kilogram (mg/kg) in rabbits to 420 mg/kg in mice. Pathological changes were seen in the respiratory system, liver, and kidneys following EDB exposures of varying duration. EDB vapor in excess of 200 ppm resulted in death of rats from respiratory or cardiac failure within 24 hours of exposure along with liver and kidney damage. In subchronic studies, histopathological effects on the nasal cavity were reported in rats and mice exposed to EDB at 10 ppm and above but not at 3 ppm. Effects on relative kidney weights were seen at all exposed levels.

In rats, rabbits, guinea pigs, and monkeys, exposure to EDB was tolerated without adverse effects at a concentration of 25 ppm for six months, but a concentration of 50 ppm produced lung irritations and damage to the liver and kidneys.

4.2 Human

EDB causes skin irritation, inflammation, and blistering following dermal exposure. Exposure to the vapor can cause respiratory tract inflammation, anorexia, headache, and throat and eye irritation as reported in a worker from occupational exposure to unknown concentrations. Respiratory irritation was reported in workers in a chemical plant at about 75 ppm, and gastrointestinal discomfort and vomiting were probably induced by short exposures at 100-200 ppm for up to 1 hour, or by lower exposures over longer periods of time (NIOSH, 1977).

5. Pharmacokinetics

Studies on the pharmacokinetics of EDB have been reviewed by Rannug (1980) and those studies which contain the results used for discussion in this section are cited there. Tissue distribution in mice showed that 24 hours after an intraperitoneal (ip) injection of 40 mg/kg of [^{14}C]-EDB, all tissues showed less than 1% retention of radioactivity except for the whole blood (6.2%). The intestines and kidneys had most of the radioactivity at one and three hours after the injection. In the guinea pigs, tissue samples collected 4-72 hours after an ip injection of 30 mg/kg of [^{14}C]-EDB showed that the highest concentration of radioactivity was in the kidneys, liver, and adrenal glands, with the former two showing the highest percentage of the administered dose. About 66% of the injected dose was excreted in the urine of the guinea pigs over the 72-hour period, and 40% was excreted as metabolites in the urine of the mice. After oral administration, S-(2-hydroxyethyl)cysteine and N-acetyl-S-(2-hydroxyethyl)cysteine and the corresponding S-oxides were identified as urinary metabolites in rats. Bromoacetaldehyde was identified as the metabolite formed by the phenobarbital-induced microsomal enzymes in the presence of nicotinamide adenine dinucleotide phosphate (reduced) (NADPH). The identification of S-(2-hydroxyethyl)glutathione and S,S'-ethylene-bis-glutathione as metabolites suggested an activation of EDB through conjugation with glutathione, producing the S-(2-haloethyl)glutathione

conjugate and/or the corresponding cysteine conjugate as the mutagenic metabolite (See Section 7. Mutagenicity).

There is no available evidence that would demonstrate differences in pharmacokinetics of EDB between the experimental animals and humans and that could be used for corresponding adjustments in extrapolating from animals to humans. For the purpose of the present health assessment, observations made in experimental animals are considered not to be significantly different from those expected in humans, unless otherwise specified.

6. Reproductive Effects/Teratogenicity

6.1 Animal

Studies with bulls, rams, chickens, and rodents have shown that EDB may cause adverse reproductive effects. Most of the relevant studies in publication have been reviewed by OSHA (P.45966 under III [c] [2]. Animal Studies, Appendix A). This section provides a brief overview of the findings summarized by OSHA, and summarizes two new studies not covered by them.

In bulls given oral doses of 2 mg/kg/day, the effects seen were reduced sperm density and motility, abnormal sperm morphology, and changes in the histology of the testes (Amir and Volcani, 1965). Other effects were seen in the sperm of rams, litter size of rats and mice, and reproductive system of female chickens. Other studies with EDB given

at 10 to 150 mg/kg to rats or mice all did not show effects on fertility or dominant lethal effects.

In two teratology studies (Short et al., 1976; 1978) in which rats and mice were exposed to EDB at a concentration ranging from 0 to 80 ppm, the findings suggest that the effects seen could be secondary to maternal toxicity. Barlow and Sullivan (1982) concluded from the above studies that EDB does not appear to cause any increase in the incidence of major malformations in rats, but they pointed out that there was an overall increase in the types of anomalies seen at 32 ppm and that the possibility of a direct effect of EDB on anomalies seen remains equivocal.

Prenatal exposure to EDB has also been reported to produce alterations in the behavior in the offspring of rats (Smith and Goldman, 1983; Fanini et al., 1984). In the study of Smith and Goldman (1983), pregnant rats were exposed to EDB for 4 hrs/day, 3 days/week, from day 3 to day 20 of gestation at an inhalation concentration of 0, 0.43, 6.67, or 66.67 ppm. At the two higher levels of exposure, there was an increase in defecation during exposure, decreased gestational weight gain, and enhanced rotorod performance and T-maze brightness discrimination acquisition in the offspring, with a greater effect seen in the highest treatment group. The authors suggested that behavioral effects may be secondary to stress reactions in the mothers.

Fanini et al. (1984) studied the effects of EDB on the male rats through the behavioral assessment of their F_1 progeny. Groups of 6 or

more male rats were treated ip with a daily dose of 1.25, 2.5, 5.0, or 10.0 mg/kg. After the last injection, the males were mated to untreated virgin females at four and nine weeks. The behavioral development was assessed using a test battery including the assessment of simple reflexes, motor coordination, and locomotor activity. Results obtained showed significant impairment in swimming performance (direction, head angle, limb movement) of the offspring from paternal EDB exposure, and the manifestation of the impairment was dependent upon the time of breeding following exposure and the particular component of swimming behavior analyzed. The significant effects did not always follow a linear dose-response function, an observation frequently encountered in behavioral teratology. The most consistent behavioral abnormalities were observed in the open field activity test in which the amount of ambulation in the open field was significantly suppressed in the offspring of EDB-treated males at dosages as low as 1.25 mg/kg/day.

The most sensitive study for which reproductive toxicity of EDB has been observed is that of Fanini et al. (1984). The lowest level at which adverse behavioral effects were observed in the offspring of treated male rats was 1.25 mg/kg/day. Similar effect levels were reported for bulls for sperm abnormalities (2 mg/kg/day). Other studies showed effects occurring at levels ranging from 5.2 to 133.2 mg/kg/day.

For the purpose of this assessment, effects observed following exposure to EDB via the intraperitoneal or oral route are not considered to

differ significantly from those which might occur after exposure via the respiratory route, particularly at the relatively low levels used in the studies. Since ambient levels of around 7 ppt are equivalent to daily doses of 1.8×10^{-5} mg/kg (60-kg person), ambient levels provide doses about 70 thousand times less than the lowest-observed-effect level (LOEL) of Fanini et al. (1984) and one hundred thousand times below the LOEL of Amir and Volcani (1965). Since reproductive effects are likely to have thresholds, the safety factor obtained should be sufficient to protect against reproductive effects occurring from ambient exposures to EDB.

6.2 Human

Human epidemiological studies do not show an effect on reproduction resulting from exposure to EDB. The findings and limitations of the studies have been discussed (P.45963 under III [c] [1]. Reproductive Effects, Appendix A). At the same time, these studies, because of their limitations, do not rule out the possibility that EDB may have an adverse effect on the humans. Suggestions of a potential toxic effect of EDB came from two studies. The study of EDB-production workers at the Houston Chemical Company by NIOSH (1977) revealed a significant increase in luteinizing hormone. There was, however, no overall significant effect in sperm count or testicular toxicity. Wong et al. (1979), who reported a significant decrease in standardized birth ratio in one (Houston Chemical) of the four plants studied, indicated that the observations made could not be attributed to differences in

exposure levels because the average exposure level to EDB was not higher at this plant compared with other plants. No exposure data were available on an individual basis for this plant, and a higher percentage (33%) of the couples from the Houston Chemical plant had a sterilized partner when compared to the national survey (30%).

Due to the lack of adequate human data, the quantitative assessment for the potential human reproductive effects of EDB will rely on the use of animal data.

7. Genotoxicity

Studies on the mutagenic potential of EDB have been reviewed by OSHA (P.45967 under III [D]. Mutagenic and Cytogenic Effects, Appendix A), IARC (1977, 1982), and Rannug (1980). Specific references can be obtained from these reviews.

EDB was shown to have genotoxic activity in in vitro and in vivo systems. It can induce gene mutation in bacteria, fungi, plants, insects, and mammalian cell systems. Chromosomal effects were found in plants and DNA damage in mammalian cell systems treated with EDB. Interactions with nuclei acids and/or proteins of virus and mammals were observed. EDB is a direct-acting mutagen in microbial test systems, but it can also be bioactivated in the presence of a metabolizing system (Rannug, 1980). The corresponding monohaloaldehyde and haloethyl glutathione conjugate derived from EDB are believed to be

involved in the genotoxic effect and macromolecular binding of this chemical. Bromoacetaldehyde is a mutagen and binds to a greater extent to DNA and protein than EDB in vitro. The EDB-glutathione conjugate is more mutagenic than EDB itself in the Ames test. The conjugates may also play a role in the "direct" mutagenic effect of EDB on Salmonella because the bacteria exhibit glutathione-S-transferase activity but no mixed-function oxygenase activity.

The ability of EDB to induce gene mutation and demonstrate genotoxicity in test systems is suggestive of its potential to induce mutations in human populations, but there is no available evidence to provide an adequate quantitative assessment of the relative risks to humans. Staff of DHS agrees with the IARC (1982b) that the evidence for the genotoxicity of EDB is sufficient.

8. Carcinogenicity

8.1 Animal

EDB is an animal carcinogen producing cancer in rats and/or mice by inhalation, oral, and dermal routes (P.45960 under III [B] [1]. Animal Studies, Appendix A). It produced tumors at the site of contact and also at sites remote from the inital site of application. Contact-site tumors included forestomach tumors in the gavage study, nasal tumors in the inhalation studies, and skin tumors in the dermal study. Other

systemic tumors, notably the hemangiosarcomas in both the gavage and inhalation studies, were also seen. There is no evidence to suggest that EDB has a threshold for its carcinogenic activity, and it should be treated as having no threshold for its carcinogenic effect.

8.2 Human

The studies on the potential carcinogenicity of EDB in humans are discussed in Section 9.

9. Epidemiology

Only one peer-reviewed epidemiological study of EDB-exposed humans has been published (Ott et al., 1979). The staff of the DHS agrees with the authors of this study of 161 workers when they say, "Findings of this investigation neither rule out nor establish EDB to be a human carcinogen." As mentioned by the staff who prepared the OSHA document, the statistical power of this study and several non-peer-reviewed studies is inadequate. (See Appendix B for more details.) We must therefore rely on animal bioassays for identification of EDB as a potential human carcinogen and for quantitative risk assessment.

10. Thresholds

For toxicologic purposes, a threshold dose is one below which a specified outcome does not occur. The self-propagating, clonal nature of tumor growth and development from a single damaged cell however suggests that the effective dose for carcinogenesis may be so low as to be indistinguishable from zero. While threshold models (based on detoxification enzyme saturation, the existence of DNA repair mechanisms, recurrent cytotoxicity) have been proposed, none has been convincingly demonstrated.

An "epigenetic mechanism" that could theoretically embody threshold doses has been invoked to explain the carcinogenic action of substances that do not directly produce genetic damage in short-term tests. However, neither short-term tests nor non-linearities in dose-response curves from animal bioassay can reliably distinguish between "genetic" versus "epigenetic" carcinogenesis primarily because of the limited sensitivities of the experimental methodologies. DHS staff agrees with the conclusion of the IARC (1983) that there is insufficient evidence at present to justify creating separate classes of carcinogens (based on mechanism) for which different risk assessment methods would be used. In any case, in view of the strong evidence for EDB's genotoxicity, it would be inappropriate to suggest that this substance's carcinogenicity is due to an epigenetic mechanism.

Thus, in the absence of compelling evidence to the contrary, DHS treats carcinogenesis as a non-threshold phenomenon.

11. Cancer Risk Assessment

OSHA provided the results of eight risk assessments performed on EDB based on a series of different models and estimates for worker exposure (P.45969 under IV. Quantitative Risk Assessment for EDB, Appendix A). OSHA's conclusion was that in spite of variations in the models and methods used for analyzing the data (combining studies, different tumor sites, and scaling factors), all results indicate an extremely high excess risk at the permissible level of 20 ppm in the workplace (Appendix A, P.45973, Table 4).

At 20 ppm, the excess cancer risk (the rate at which cancer would occur over the normal background level of 25%) is estimated to range from 70 to 999 cases per 1000 people exposed. The estimated risk depends heavily on the model used and the choice of tumor data upon which the quantitative risk assessment is based. OSHA endorsed Brown's approach to the quantitative assessment of the risk from exposure to EDB. This assessment suggested an estimate of 725 excess deaths per 1000 based on the nasal tumors. "OSHA believes that the multistage model (and one-hit model as a special case) is the most appropriate model for the prediction of excess cancer risk from EDB." OSHA also concluded that "...expressing dose in parts per million (ppm) or a scaling factor of one was the 'best choice' for nasal tumors". OSHA also stated, "The

choice of hemangiosarcoma data for the assessment was particularly prudent".

Although the staff of DHS believes that Brown's approach and document is well thought out, a critical point that DHS disagrees with is Brown's use of combined tumor data from several different studies. This approach dilutes the calculated risk and is not the most health conservative one. The use of the most sensitive site, sex, and species for purposes of risk assessment is based on the concept of the greater genetic diversity of humans as compared with that of inbred laboratory animals. DHS did not use the other risk assessments presented in the OSHA document but performed an independent one because the others differ from the DHS risk assessment in the choice of tumor type (OSHA in-house), scaling factor (Cal-OSHA, SRI, EPA-CAG), data set from one or two studies (SRI, Brown), animal bioassay (EPA-CAG, 1980) and data base (bioassay vs. epidemiology; EPA-CAG, 1978). In addition, these risk assessments did not use the Weibullized-Multistage model that DHS used.

The staff of DHS performed its own risk assessment consistent with prior DHS procedures incorporating many of the recommended points in the OSHA review of prior risk assessments. Risks were calculated for ambient concentrations of 10 ppt and for occupational exposures of 20 ppm (3.9 ppm as a lifetime time-weighted average) for comparison with those provided in the OSHA document. Three low-dose extrapolation models were used: the multistage, the Weibull-multistage (time-dependent multistage which was not utilized in any prior risk

assessment on EDB), and the probit model. The Crump Global 79 program was used for the multistage model. The Howe and Crump Weibull 82 program was used for the time-dependent multistage model in which risk is considered a function of both time and dose. This model corrects for intercurrent mortality by incorporating survival times and calculates latency periods. Data input for Weibull 82 uses the time of death of each animal and considers whether the animal had the tumor of concern at necropsy. The Kovar and Krewski program Risk 81 is used for the Probit model. This dichotomous response model assumes that the dose-response relationship is a cumulative normal distribution and thus that the log of the dose versus the probit (normal equivalent deviate + 5) is linear.

Considerations included in the choice of low-dose extrapolation models are: simplicity, interpretability, biological plausibility, sensitivity to differences in the observable range, and ability to take into account timing of exposure, latency periods, and competing risks. The underlying principle behind the use of the multistage model is the biologic plausibility of the theory that carcinogenesis is a multistage process. Additionally the direct interpretability of its coefficients and the fact that it is linear at low doses make it a reasonable choice. The Weibull-multistage model has these same properties as the simple multistage model and, in addition, it incorporates a latency period and utilizes fully the data on survival times which are available on the NCI carcinogenesis bioassays.

DHS staff examined risk estimates for all three models for nasal malignancies (a site of first contact in the NCI inhalation study of male rats) and for hemangiosarcomas in the NCI study of female mice (a remote-site cancer which appeared in both gavage and inhalation studies). The original bioassay cancer attack rates are shown in Table 1. Appendix D provides calculations for interspecies scaling and dose using time-weighted concentrations.

Table 1

Cancer Attack Rate in Two EDB Inhalation
Bioassays Carried Out for the National Cancer Institute

	Experimental Groups (50 animals in each)		
	Control	10 ppm	40 ppm
Tumor/Species			
Nasal Malignancies*			
Male Rat	0%	46%	76%
Hemangiosarcomas			
Female Mice	0%	24%	46%

* Adenocarcinomas, carcinomas, and squamous cell carcinomas

The results of the risk assessments are shown in Table 2. The theoretical excess lifetime risks for the 1983 permissible exposure limit (PEL) of 20 ppm are listed to allow comparison with the risk assessments presented in the OSHA document. The theoretical risks in the DHS risk assessment are similar to those of the other risk assessments (Appendix A, P.45973, Table 4) which are in the range of

hundreds of cases per thousand. One exception is Brown's risk estimates based on hemangiosarcomas showing less than 200 cases per million. It should be noted that none of the workers studied have ever had consistent exposure as high as this so that, to our knowledge, there has been no opportunity to observe the human effect of such high exposures. The same models extended downward to ambient levels of 10 ppt provide lifetime risk estimates ranging from 0 (zero) to 5.53 cases per million.

Table 2
Risk Estimates for Cancer Death Rates
Due to EDB Exposures

Species/Tumor	Model	UCL*/MLE**	20 ppm Occupational Exposure (PEL)***	10 ppt Community Exposure
Male Rats				
Nasal Malignancies	Weibull-Multistage	95% UCL	985/1000	5.53/million
		MLE	916/1000	2.85/million
	Multistage	95% UCL	708/1000	3.15/million
		MLE	627/1000	2.53/million
	Probit	95% UCL	721/1000	$0^{\S}$/million
		MLE	638/1000	$0^{\S}$/million
Female Mice				
Hemangiosarcomas	Weibull-Multistage	95% UCL	732/1000	3.23/million
		MLE	549/1000	2.03/million
	Multistage	95% UCL	406/1000	1.34/million
		MLE	328/1000	1.02/million
	Probit	95% UCL	438/1000	$0^{\S}$/million
		MLE	357/1000	$0^{\S}$/million

* UCL - Upper confidence limit
** MLE - Maximum likelihood estimate
***PEL - Permissible Exposure Limit (Proposed for revision by OSHA, 1983. See Appendix A.)
§= Predictions for probit model ranged from $0\text{-}10^{-31}$

12. Compatibility of Animal Risk Assessments and Epidemiological Results

EDB is a potent carcinogen in animals, causing contact carcinogenesis for skin, forestomach, and nasal cavity in dermal, gavage, and inhalation studies, respectively. Cancers were found in sites remote from the initial site of contact in all three kinds of studies. As has been seen above, extrapolations from the animal cancers, both of first contact and remote sites, suggested high theoretical lifetime risks for occupational exposures to EDB at the PEL of 20 ppm (PEL used for risk assessments as presented by OSHA and proposed for revision in 1983, See Appendix A). These extrapolations prompted Ramsey et al. (1978) to see whether the one-hit model used by the EPA provided estimates which were compatible with the negative results from Ott's study of 161 workers. They concluded that the risk assessment was not compatible since the risk assessment indicated that 85 of the workers instead of the 8 observed would have been expected to develop cancer during the period of observation.

In Appendices C and D DHS staff reviewed the study by Ott et al. and applied the multistage model estimates based on the forestomach cancer (gavage) and nasal tumors (inhalation). This is done to make sure that the DHS risk assessments are not incompatible with the epidemiological data. The results show that the same multistage model which predicts 3.2 cases per million from a lifetime exposure to 10 ppt predicts only a few extra cases of cancer in this small cohort of 161 workers whose effective time-weighted lifetime exposure was in the parts per billion

range. The predicted added risk as well as the relative risk is very close to what was in fact observed and is certainly within the 95% confidence interval of this small study.

Furthermore, the Weibull-multistage model or probit model applied to nasal malignancies, or any of these three models applied to the hemangiosarcoma data, would also yield predictions which are not discrepant with the observed worker mortality.

The risk estimates in Table 2 that are extrapolated from animal data using three models can therefore be considered reasonable in that they are not incompatible with the human epidemiologic results, and DHS staff thus concludes that they can all be used with scientific justification. The theoretical bases for the multistage model and Weibull-multistage model, however, are sounder than for the probit model, and the DHS recommends using the estimates from both these former two models.

13. Conclusions

On the basis of the findings discussed in the preceding sections, the following can be concluded:

1. No systemic toxicity or reproductive effects would be expected to result from exposure to EDB at an ambient air concentration of 7 ppt or less.

2. The DHS staff agrees with the IARC that there is sufficient evidence to show that EDB is carcinogenic in animals and that in the absence of adequate data in humans, it is reasonable, for practical purposes, to regard the chemical as if it presented a carcinogenic risk to humans.

3. EDB and its metabolites are genotoxic.

4. There is no evidence to demonstrate that the carcinogenicity of EDB has a threshold and EDB's carcinogenic activity should be treated as having no threshold.

5. An excess lifetime risk value between 1.02 and 5.53 per million for exposure to an air concentration of 10 ppt EDB is recommended. The corresponding theoretical lifetime risk values at the present ambient levels of about 7 parts per trillion are estimated as being between 1 and 4 per million.

Federal Register

Friday
October 7, 1983

Part VI

Department of Labor

Occupational Safety and Health Administration

Occupational Exposure to Ethylene Dibromide; Notice of Proposed Rulemaking

DEPARTMENT OF LABOR

29 CFR Part 1910

[Docket No. H-111]

Occupational Exposure to Ethylene Dibromide

AGENCY: Occupational Safety and Health Administration [OSHA], Labor.

ACTION: Notice of proposed rulemaking.

SUMMARY: By this notice, the Occupational Safety and Health Administration, [OSHA] is proposing to revise the present occupational health standard regulating employee exposure to ethylene dibromide [EDB], 29 CFR 1910.1000, Table Z-2.

The proposed standard mandates a reduction in the premissiable exposure limit from 20 parts per million parts of air to 0.1 parts per million, restricts dermal exposure and sets requirements for exposure monitoring, methods of control, personal protective equipment, hygiene practices, medical surveillance and employee training and education.

The proposed revision is based on OSHA's determination that the present premissible exposure limit (PEL) for EBD of 20 parts per million (ppm) as an 8-hour time weighted average (TWA) exposure does not provide adequate protection against cancer and other adverse health effects.

DATES: Written comments on these rules must be postmarked by November 21, 1983. Objections and requests for a hearing must be postmarked by November 21, 1983.

ADDRESSES: All comments, objections and hearing requests should be sent to the Docket Officer, Docket H-111, U.S. Department of Labor, Occupational Safety and Health Administration, 200 Constitution Avenue, N.W., Room S-6212, Washington, D.C. 20210; (202) 523-7894.

Written comments received will be available for inspection and copying in the Docket Office, Rm S-6212 at the above address.

FOR FURTHER INFORMATION CONTACT: Mr. James F. Foster, Office of Public Affairs, U.S. Department of Labor, Occupational Safety and Health Administration, 200 Constitution Avenue, N.W. Room N3718., Washington, D.C. 20210; (202) 523-8151.

SUPPLEMENTARY INFORMATION: As an aid to the reader, the following is an outline of the contents of this Federal Register Notice.

I. Pertinent Legal Authority

Authority for issuance of this standard is found primarily in sections 6(b), 8(c), and 8(g)(2) of the Occupational Safety and Health Act of 1970 (the Act), 29 U.S.C. 655(b), 657(c), and 657(g)(2). Section 6(b)(5) governs the issuance of occupational safety and health standards dealing with toxic materials or harmful physical agents. Section 3(8) of the Act, 29 U.S.C. 652(8), defines an occupational safety and health standard as:

> (A) standard which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide a safe or healthful employment and places of employment.

The Supreme Court has said that section 3(8) applies to all permanent standards promulgated under the Act and requires the Secretary, before issuing any standard, to determine that it is reasonably necessary and appropriate to remedy a significant risk of material health impairment. *Industrial Union Department* v. *American Petroleum Institute*, 448 U.S. 607 (1980).

The "significant risk" determination constitutes a finding that, absent the change in practices mandated by the standard, the workplaces in question would be "unsafe" in the sense that workers would be threatened with a significant risk of harm. *Id.* at 642. This finding is not unlike the threshold finding that a substance is toxic or a physical agent is harmful. *Id.* at 643, n. 48. A significant risk finding, however, does not require mathematical precision or anything approaching scientific certainty if the "best available evidence" does not warrant that degree of proof. *Id.* at 655-656; 29 U.S.C. 655(b)(5). Rather, the Agency may base its finding largely on policy considerations and has considerable leeway with the kinds of assumptions it applies in interpreting the data supporting it. *Id.* The Court's opinion indicates that risk assessments, which may involve mathematical estimates with some inherent uncertainties, are a means of demonstrating the existence of significant risk.

After OSHA has determined that a significant risk exists and that such risk can be reduced or eliminated by the proposed standard, it must set the standard "which most adequately assures, to the extent feasible on the basis of the best available evidence, that no employees will suffer material impairment of health * * *." (Section 6(b)(5) of the Act). The Supreme Court has interpreted this section to mean that OSHA must enact the most protective standard possible to eliminate a significant risk of material health impairment, subject to the constraints of technological and economic feasibility. *American Textile Manufacturers Institute, Inc.* v. *Donovan*, 452 U.S. 490 (1981). The Court held that "cost-benefit analysis is not required by the statute because feasibility analysis is." *Id.* at 509.

Authority to issue this standard is also found in section 8(c) of the Act. In general, this section empowers the Secretary to require employers to make, keep, and preserve records regarding activities related to the Act. In particular, section 8(c)(3) gives the Secretary authority to require employers to "maintain accurate records of employee exposures to potentially toxic materials or harmful physical agents which are required to be monitored or measured under section 6." Provisions of OSHA standards which require the making and maintenance of records of medical examinations, exposure monitoring, and the like are issued pursuant to section 8(c) of the Act.

The Secretary's authority to issue this proposed standard is further supported by the general rulemaking authority granted in section 8(g)(2) of the Act. This section empowers the Secretary "to prescribe such rules and regulations as he may deem necessary to carry out (his) responsibilities under the Act"—in this case as part of or ancillary to, a section 6(b) standard. The Secretary's

responsibilities under the Act are defined largely by its enumerated purposes, which include:

• • • [E]ncouraging employers and employees in their efforts to reduce the number of occupational safety and health hazards at their places of employment, and to stimulate employers and employees to institute new and to perfect existing programs for providing safe and healthful working conditions [29 U.S.C. 651(b)(1)];

• • • [A]uthorizing the Secretary of Labor to set mandatory occupational safety and health standards applicable to business affecting interstate commerce, and by creating an Occupational Safety and Health Review Commission for carrying out adjudicatory functions under the Act; [29 U.S.C. 651(b)(3)];

• • • [B]uilding upon advances already made through employer and employee initiative for providing safe and healthful working conditions [29 U.S.C. 651(b)(4)];

• • • [P]roviding for the development and promulgation of occupational safety and health standards [29 U.S.C. 651(b)(9)];

• • • [P]roviding for appropriate reporting procedures with respect to occupational safety and health which procedures will help achieve the objectives of this [Act] and accurately described the nature of the occupational safety and health problems [29 U.S.C. 651(b)(12)];

• • • [E]xploring ways to discover latent diseases, establishing causal connections between diseases and work in environmental conditions • • • [29 U.S.C. 651(b)(6)];

• • • [E]ncouraging joint labor-management efforts to reduce injuries and diseases arising out of employment [29 U.S.C. 651(b)(13)];

• • • [A]nd developing innovative methods, techniques, and approaches for dealing with occupational safety and health problems [29 U.S.C. 651 (b)(5)].

Because the ethylene dibromide standard is reasonably related to these statutory goals, the Secretary finds that this standard is necessary to carry out his responsibilities under the Act. In addition to its status as a section 6(b) standard, it also falls within the broader class of section 8 regulations.

II. General

A. Chemical Identification

Ethylene dibromide (Chemical Abstract Services Registry Number 106-93-4) is a colorless, non-flammable liquid at room temperature with a distinctive, mildly sweet odor detectable in air at levels ranging from 10-25 parts per million. It turns brown on exposure to light and reacts as an alkylating agent, liberating bromine. Synonyms for ethylene dibromide include EDB, 1,2-dibromoethane, ethylene bromide, sym-dibromoethane and glycol bromide. It has a chemcial formula of $Br\text{-}CH_2\text{-}CH_2\text{-}Br$, with a molecular weight of 187.9.

B. Production and Use

Ethylene dibromide (EDB) is a clear and colorless liquid that has a number of applications. EDB is produced commercially by reacting gaseous ethylene with liquid bromine. Its primary use is as a scavenger in leaded gasoline to prevent the buildup of lead oxides from tetraethyl lead in automobile engines. EDB is also used as a pesticide, as an intermediate in the synthesis of dyes and pharmaceuticals, and as a solvent for resins, gums, and waxes. Most potentially significant exposures to EDB occur in the industries or industry sectors where it is manufactured, used in the manufacturing and blending of antiknock compounds, formulated for use as a pesticide, or used as a fumigant on citrus (primarily California, Florida, and Texas), grain and papayas. EDB is also used in the fumigation of flour milling equipment. Some EDB is used in the fumigation of mangoes, etc. [See Preliminary Regulatory Impact Assessment].

The four firms that currently produce EDB in the United States are PPG Industries (PPG) [1] Ethyl Corporation (Ethyl), Great Lakes Chemicals Corporation (GLCC), and the Dow Chemical Corporation (Dow). As a result of the declining use of leaded gasoline, it is probable that one or two firms will cease production of EDB by 1990.

The available information indicates that a total of 90 production workers at all four plants are exposed to EDB on daily basis continuously, and that up to 400 industrial production workers are exposed to EDB on a periodic basis in manufacturing. These employees also include maintenance personnel providing maintenance services for plant operations as well as other personnel who occasionally may be exposed for short periods of time, but not on a daily basis.

Employees in the EDB manufacturing industry generally perform one of five different functions. At the Ethyl Corporation, the functions are divided into four job categories which include a crew leader, a control room operator, a loader, and surveillance technician. The crew leader is responsible for the manufacturing and oversees the production of EDB, vinyl bromide, bromine, and sulfur.

EDB is used in the manufacturing of antiknock additives for gasoline. These additives vary in composition with more than 100 different blends being produced (Ex. 7-2 p.7). A typical gasoline blend, however, contains ethylene dibromide (17.86 percent), ethylene dichloride (18.81 percent), and various tetralkyl (methyl and ethyl) leads in a ratio of about 1:1:3. Aviation antiknock mixes contain 35.68 percent weight EDB and no EDC. In addition, some blends may contain benzene and toluene. The blending process does not involve the chemical reaction of ethylene dibromide with the other compounds of the mix, but is a physical blending of the constituents.

Employees exposed to EDB in the manufacturing of antiknock compounds and their blending, generally are exposed to EDB in the control room, production loading and peripheral operations. As of January 1, 1982, the following four firms supplied antiknock packages: E. I. Dupont de Nemours and Company Inc., (Dupont), Ethyl Corporation (Ethyl), Nalco Chemical Company (Nalco), and PPG Industries (PPG). At Nalco, for example, some of the jobs where employees may be exposed to EDB include shift superintendent, a blend operator, a material handler, and a laboratory technician. The following are some of the jobs and operations that can result in exposure to EDB:

a. Blend operator—unloading all liquid raw materials, takes quality control samples, blends products and loads tank cars.

b. Material handler—assists the blend operator in all duties.

c. Laboratory technician—conducts quality control tests on raw materials and finished products.

EDB is used with other chemicals in the formulation of pesticides. The consumption of EDB for use in pesticides has increased from about 5 million pounds in 1976 to an estimated 13-15 million pounds in recent years. A total of 18 firms with 20 plants formulate pesticides containing EDB, including three of the four EDB manufacturers identified earlier. These firms either formulate pesticides containing EDB or repackage EDB-containing pesticides that have been blended previously. The EDB pesticide formulation process involves a batch operation in which liquid EDB is blended with other liquid active or inert ingredients and then packaged into containers. In most plants, this is a partially closed system, with completely closed blending operations and open packaging (or filling) operations. In addition to the EDB blending and filling operations described above, plant production workers may be exposed to EDB during maintenance, laboratory sampling and analysis, and warehouse activities.

[1] PPG Industries is no longer manufacturing EDB.

To be more specific EDB is obtained in 30-gallon or 55-gallon drums, in rail cars or tank trucks. It is mixed with other active or inert ingredients and the formulated pesticides are then repackaged. In about 50 percent of all EDB pesticide formulation plants, including both small and large plants, EDB is pumped from the container in which it was received to a blending or mixing tank. Other ingredients are also pumped into the blending tank. The ingredients are sometimes agitated or blended with a mixer, but in most cases, the force of the pumping action blends the ingredients sufficiently. The final product is then packaged into one-gallon or five gallon pails, 30-gallons or 55-gallon drums, cylinder tanks ranging in size from eight pounds to 144 pounds, or tank trucks. There are many opportunities for EDB exposure during formlation. While exposures vary from plant to plant, the following formulation operations frequently result in exposure to EDB:

a. Pumping EDB to storage tanks;
b. Pumping EDB from tanks or drums to blending tanks or drums;
c. Filling EDB pesticide containers (pails and drums);
d. Loading tank trucks;
e. Capping EDB pesticide containers (pails and drums);
f. Maintaining, repairing, cleaning, and/or disposing or drums, tanks, pumps, and equipment;
g. Taking and analyzing quality control samples; and
h. Working in warehouse operations.

The Animal, Plant, and Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA) requires citrus and other fruits to be fumigating if the citrus is transported interstate from a regulated area to prevent the spread of the fruit fly.

The handling process for fresh citrus includes packing the citrus, fumigated and hauling the fumigated produce either to nearby export warehouses or to distant warehouses in other citrus-growing regions. The initial operations preceding the packing of the citrus are comparable in Texas and Florida, but packed Florida fruit is loaded into trailer trucks and hauled to central, state-operated fumigation chambers, whereas Texas citrus is fumigated in privately operated chambers at the packinghouse.

Employee exposure to EDB following fumigation is related to the rate at which the adsorbed EDB offgasses from citrus. Offgassing begins immediately following fumigation and will continue for up to 14–21 days. Another source of exposure is the citrus cartons which also adsorb EDB and continue to offgass for appreciable periods following completion of the fumigation cycle.

The proposed standard directly affects truckers who haul fumigated fresh citrus, and longshoremen and warehousemen who are exposed to EDB at the port facilities. In addition the agency has found residual EDB on the surface of citrus after fumigation. This residual may be an additional source of exposure.

Liquid grain fumigants containing EDB are used to prevent insect infestation in stored grain. Unfortunately, little published data are available on the amount of grain fumigated with EDB, on the quantity of EDB formulations used in the facilities using those fumigants, or on the number of worker exposed. Grain storage facilities are either "on-farm" sites or "off-farm" sites. The latter include country elevators, subterminal and terminal elevators, port elevators, and grain stored by flour mills and feed processors.

As explained in the Regulatory Impact Assessment, EDB is a favored fumigant in small grain storage facilities because these small facilities usually are not well sealed. EDB is retained by the grain longer than other carbon tetrachloride based fumigants and the grain in these open facilities can remain uninfested longer.

EDB has been used over 20 years as a "spot fumigant" for the control of insect populations that invade flour milling equipment. Flour and cereal grains tend to collect the many ledges and obstructions within mill machinery and represent the primary areas of insect infestation. EDB is considered an essential ingredient in spot fumigation. When applying EDB "spot fumigants," the flour milling and cereal handling equipment is run until it is as empty as possible, leaving only small quantities of grain trapped in the machinery. The EDB fumigant is then applied with a gun that releases the fumigant into specially designated holes in the grain mill equipment. The facility is then shut down for about 24 hours, after which the equipment is either aired out or placed back in operation without aeration. Using this procedure, worker exposure in the mill is reduced considerably, but is not totally eliminated.

EDB is a fumigant used to control Mediterranean Fruit Flies in and on Papaya leaving Hawaii. Papaya is fumigated in large containers and then is removed from the containers, culled, washed and treated with a fungicide and then is packed in boxes for shipment. Generally, the boxes are loaded into refrigerated shipping containers and transported to California by sea. Five of the seven fumigation sites are located in Hilo, on the Island of Hawaii. The production operations consist of fumigating, packing, and shipping the harvested papaya. Exposure is of course related directly and indirectly to fumigation operations with the frequency and intensity of fumigation directly affecting worker exposure.

Employee exposures to EDB occur during the fumigation process and the resulting offgassing of fruit during sorting/packing, storing and transportation. Many of the same exposure possibilities mentioned in connection with the fumigation of citrus also occur with fumigated papaya.

C. Present Standard

The premissible exposure limit (PEL) for occupational exposure to ethylene dibromide is found in Table Z–2 of 29 CFR 1910.1000. The standard provides that an employee's airborne exposure to ethylene dibromide, in any 8-hour workshift of a 40-hour workweek shall not exceed an 8-hour time weighted average (TWA) limit of 20 parts per million (ppm). Further, an employee's exposure to ethylene dibromide shall not exceed a ceiling concentration of 30 ppm at any time during an 8-hour shift, except for a maximum duration of 5 minutes, when the "acceptable maximum peak" concentration shall not exceed 50 ppm.

The standard provides that administrative or engineering controls must be implemented to reduce exposure to within the PEL whenever feasible. When such controls are not feasible to achieve full compliance, protective equipment or any other protective measure shall be used to keep the exposure of employees to EDB within the limits prescribed.

The current standard for EDB was adopted in 1971 as a national consensus standard, under Section 6(a) of the Occupational Safety and Health Act of 1970. (84 Stat. 1592; 29 U.S.C. 655). The source of the standard was the American National Standards Institute (ANSI Z 37.31–1970). The ANSI exposure limits were intended to protect workers from injury to the lungs, liver, and kidneys which had been observed from excessive acute, or chronic exposures to EDB in humans and experimental animals. The potential for EDB to cause cancer or reproductive damage was not a basis for the establishment of the current permissible exposure limit.

D. Background

On December 14, 1977, EPA issued a notice of Rebuttable Presumption Against Registration and Continued

Registration (RPAR) of pesticide products containing EDB (42 FR 63134), under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended (7 U.S.C. 136 *et seq.*). EPA subsequently proposed immediate cancellation of the EDB registration for stored grain and cancellation of the EDB registration for post-harvest fumigation of citrus, tropical fruits and vegetables as of July 1, 1983 (see 45 FR 81516, December 10, 1980). EPA has, thus far, taken no final action on these proposed cancellations.

In 1977, The National Institute for Occupational Safety and Health (NIOSH) recommended that the PEL for EDB be reduced to a ceiling limit of 0.13 ppm [or 130 parts per billion (ppb)] (Ex. 4–4). NIOSH recommended revising the standard and included requirements for environmental monitoring, medical surveillance, labelling, personal protective equipment and clothing, employee training, work practices, sanitation practices, and recordkeeping requirements. This determination was based on several scientific reports which indicated that chronic exposure to EDB may lead to cancer, birth defects, sterility, damage to genetic material, and a number of other systemic effects. Following receipt of the NIOSH recommendations for a revised standard, OSHA published a request for comments and information in the Federal Register on March 17, 1978 (43 FR 11227). The request asked for comments on several general and specific issues concerning the NIOSH recommendations for a revised standard for occupational exposure to EDB. OSHA received 34 comments from individuals and companies representing a broad range of interests. These submitted comments remain part of the permanent record for EDB and will be considered in all regulatory decisions.

In addition, EDB has been the subject of three NIOSH Current Intelligence Bulletins. The first, published in 1975, alerted workers, employers and others of the preliminary results of a National Cancer Institute study indicating that EDB is carcinogenic in laboratory rodents (Ex. 4–5). The second, published in 1978, reported that a NIOSH study had found a serious toxic interaction between inhaled ethylene dibromide and ingested disulfiram in laboratory rats and recommended that no worker be exposed to both EDB and disulfiram. (Ex. 4–6) The third, dated October 26, 1981, provides recent information on EDB's potential carcinogenic risk and reaffirms the NIOSH 1977 recommended workplace exposure limit of 0.13 ppm (Ex 4–7).

In 1977, the International Agency for Research on Cancer (IARC)concluded that sufficient evidence exists that EDB is an animal carcinogen and that it probably is a carcinogen to humans based on its evidence as an animal carcinogen. IARC placed EDB is group 2B. In general, the group 2 designation signifies that the chemical, group of chemicals, industrial process or occupational exposure is probably carcinogenic to humans. The letter B added to the numerical designation is meant to indicate inadequate data is available in humans but sufficient evidence is available for animals.

In 1978, the American Conference of Governmental Industrial Hygienists (ACGIH) added ethylene dibromide to its list of industrial substances recognized to have carcinogenic potential for humans. The 1981 ACGIH list of threshold limit values [TLV] assigns no TLV for EDB exposure, but states that "no exposure or contact by any route—respiratory, skin or oral, as detected by the most sensitive methods—shall be permitted" (Ex. 4–8).

The Public Health Services Act amended in 1978 (Section 301(b)(4)) requires the Secretary of the Department of Health and Human Services to publish a list annually of "all substances which are either known to be carcinogens or which may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed * * *" In December 1981 the Secretary of Health and Human Services through the department of Public Health Services, made a determination that EDB met this criteria and included this substance in its *Second Annual Report on Carcinogens*. The report was prepared by the National Toxicology Program and its member agencies.

In July 1981, the potential health risks of EDB drew national attention as a result of the State of California, Department of Industrial Relations, Division of Occupational Safety and Health (Cal/OSHA) proposing an emergency temporary standards (ETS) for EDB of 130 ppb. (Ex. 4–3) California was concerned that the use of EDB to treat harvested fruit to prevent the spread of the Mediterranean fruit fly world result in an increased number of workers exposed to EDB.

The California Emergency standard became effective September 23, 1981 (Ex. 4–9). California based its decision to issue an ETS on the potential widspread use of EDB as a post-harvest fumigant, the large number of workers who could be exposed and the fact that the present OSHA standard does not take into account recent data concerning the carcinogenicity of EDB. The ETS was adopted as a permanent standard on January 14, 1982, and became effective on March 22, 1982. The final California standard (General Industry) Safety Order 5219 (Ex. 7–8)] for EDB received Federal approval on March 1, 1983 (48 FR 8610). The California standard requires that worker exposure to EDB shall not exceed 130 based on an 8-hour TWA and shall not exceed a 130 ppb ceiling limit based on a 15-minute sample. It also requires reporting of EDB use, emergencies, exposure monitoring, methods of compliance, personal protective equipment, training and recordkeeping.

E. Petitions for an Emergency Temporary Standard

On September 2, 1981, the International Brotherhood of Teamsters (IBT) petitioned OSHA for an emergency temporary standard for EDB which would reduce the PEL to 15 ppb as an 8-hour TWA. (Ex. 4–11) IBT members represent a large number of workers in the fruit industry, where EDB may be used to control infestation by Mediterranean fruit fly. The IBT petition was later joined by the Food and Beverage Trades Department, AFL–CIO, in a letter to OSHA dated October 5, 1981, (Ex. 4–12) and by the American Federation of Labor and Congress of Industrial Organizations [AFL–CIO] in a letter dated October 20, 1981. (Ex. 4–13) The International Longshoremen's and Warehousemen's Union (ILWU) also requested that OSHA issue an emergency temporary standard for EDB. In a letter dated October 16, 1981, the ILWU recommended an exposure limit, both as an 8-hour TWA and a ceiling concentration of 15 ppb (Ex. 4–14). In response to these petitions, OSHA reviewed the available EDB exposure information and recent scientific evidence. After careful consideration, OSHA conclude that although the available information indicated a potential health risk, it did not meet the statutory criteria necessary for issuance of an ETS within the meaning of section 6(c) of the OSH Act. Therefore it was not possible, based on the information then at hand, to establish the feasibility of, or necessity for an ETS.

OSHA acknowledged that the present PEL for EDB may not be sufficiently protective, and therefore decided to proceed with rulemaking under section 6(b) of the Occupational Safety and Health Act of 1970. An advance Notice of Proposed Rulemaking (ANPR) was published on December 18, 1981 (46 FR 1671). The notice asked interested

parties to submit comments on a number of issues which would be critical to the development of a revised standard. OSHA also initiated a series of special industrial hygiene surveys to determine the nature and extent of EDB exposure at agricultural worksites in Texas. Florida and California.

II. Health Effects

A. Acute Toxicity

EDB is a severe skin irritant which can produce blistering. Occupational exposure to EDB in air has been found to produce severe eye irritation, throat irritation, headache, depression and loss of appetite (Clin. Tox. 1979). Nasal irritation is reported from exposures of 50 ppm. Exposures to extremely high levels through inhalation, ingestion or skin contact have been shown to produce systemic damage to several organs, e.g., kidney, pancreas, spleen, heart, liver, adrenal glands and testes. Although extremely high doses produce immediate central nervous system [CNS] depression the onset of other signs and symptoms may be delayed for several hours even at lethal doses. After the signs occur, the onset of respiratory failure and death is very rapid, usually in terms of hours. Chronic exposures to levels above the current OSHA standard of 20 ppm produce acute poisoning which indicate that either the compound or its effects are cumulative.

Eye irritation from EDB has been evaluated in rabbits (Rowe et al. 1952). Acute exposure produced pain and conjunctival irritation which lasted for about 24 hours. There was slight necrosis of the cornea but healing was rapid and complete. Dilute EDB solutions in propylene glycol were more toxic than the pure material, but healing was still complete.

EDB is rapidly absorbed through the skin in toxic amounts (Thomas and Yant 1927). Human studies show severe toxic injury due to direct contact. EDB penetrates protective clothing such as neoprene rubber and plastic gloves (Rowe et al. 1952). Serious injury has resulted when clothing, particularly shoes, which have been contaminated with EDB are worn for short periods of time (hours). The immediate signs occur in the central nervous system and at the site of exposure. In humans who survive the CNS depression, signs of systemic toxicity are delayed for up to 12 to 24 hours. The liver and kidney are major target organs in severe poisoning. Effects in humans at various doses have been reported. For example: (1) Death from oral exposure in the 150 mg/kg range: (2) systemic as well as local signs within 3 to 30 minutes of dermal exposures at 15 mg/kg but no fatalities or permanent sequelae from exposure to this level; and (3) death from inhalation doses of roughly 1000 mg/kg. Recurrent exposures at lower doses induced toxicity in a worker (Kochmann 1928). These reports characterize the toxicity of EDB to humans but they are insufficient to establish a fatal dose for dermal exposure or a no-effect dose for inhalation or oral exposure. The delay in appearance of the most severe systemic toxic effects occurs with all three dosing routes.

It may be concluded that EDB is acutely toxic. In humans doses from 15 to 150 mg/kg, EDB will produce toxic effects and death regardless of the exposure route—dermal, inhalation or oral. Absorption through the skin is rapid, on the order of minutes. The toxicity reported in the acute animal studies is consistent with these conclusions.

B. Carcinogenicity

The potential for EDB to induce cancer in mice and rats has been measured in four different bioassay studies.

1. Animal Studies

a. *Inhalation Bioassays.* In response to the Advance Notice of Proposed Rulemaking, the Dow Chemical Company submitted the results of a study of rats exposed to 0, 3, 10, and 40 ppm of EDB for 13 weeks (Exhibit 5–31). Epithelial hyperplasia of the nasal turbinates was observed in rats exposed to EDB at 10 ppm. After a post-exposure period of 88 days, reversion to the normal state had occurred. At 40 ppm, hyperplasia and non-keratizing squamous metaplasia of the nasal turbinates, decreased weight gain, and increased kidney and liver weights occurred. Most of these effects regressed after an 88 day post-exposure period. No animal was exposed to EDB for more than 13 weeks, and no animal was followed for more than 6 months. This study was not designed to evaluate the potential carcinogenic effects of chronic exposure to EDB and thus, can neither confirm or deny its carcinogenicity. The investigators, Nitschke et al., concluded that because of "the lack of any lesion subsequent to repeated exposure to 3 ppm EDB, short-term repeated exposure to these concentrations of EDB would not be expected to result in any long-term irreversible effects upon the nasal turbinates or other tissues of the body" (Ex. 5–31, p. 2). Because this was not a scientifically sound bioassay OSHA does not feel that such a conclusion is supported by this data.

The National Toxicology Program [NTP] of the National Cancer Institute [NCI] conducted an inhalation carcinogenesis bioassay for EDB (Ex 4–15). Male and female Fisher–344 rats and B6C3F1 mice were exposed to 10 and 40 ppm of EDB for periods from 78 to 103 weeks. Each treatment group consisted of 50 male and 50 female animals. The durations of exposure were 90 weeks for 40 ppm, 103 weeks for 10 ppm and 104 weeks for controls. The dose levels were selected based on a 90–day test in which 40 ppm was found to be the maximum tolerated dose.

Mice were killed by interperitoneal injection of sodium pentabarbital and examined according to standard histopathological techniques. Three cross sections were taken through the nasal cavities in order to define nasal tumors. The lengths of exposure for each species, sex and dose level were 103 weeks for low dose male rats (10 ppm), 88 weeks for high dose male rats (40 ppm), 103 weeks for low dose female rats (10 ppm), 91 weeks for high dose female rats (40 ppm), 78 weeks for lose dose male mice (10 ppm), 78 weeks for high dose male mice (40 ppm) , 103 weeks for low dose female mice (10 ppm) and 90 weeks for high dose female mice (40 ppm).

Survival rates in the high dose male and high dose female rats were significantly less than in the control or low dose groups. This could have decreased the tumor rate by shortening both the exposure time and the time available for the tumors to appear.

Survival rates in both the low dose male and female mice were significantly shortened compared to the controls. Similary this could lead to a decrease in the tumor rates by shortening the exposure time and time available for tumors to appear. The pathology reports for rats and mice describe a variety of neoplasms which were increased over the control groups.

The national Toxicology Program and NCI concluded that EDB was carcinogenic to rats, causing increased incidences of carcinomas, adenocarcinomas, and adenomas of the nasal cavity, hemangiosarcomas of the circulatory system (spleen), mesotheliomas of the tunica vaginalis (males only), adenomatous polyps of the nasal cavity (males only), fibroadenomas of the mammary gland (females only), and alveolar/bronchiolar adenomas and carcinomas (females only). EDB was also considered to be carcinogenic for mice, causing increased incidences of alveolar/bronchiolar adenomas and carrinomas, hemangiosarcomas of the circulatory

system (females only), fibrosarcomas in the subcutaneous tissue (females only), carcinomas of the nasal cavity (females only), and adenocarcinomas of the mammary gland (females only).

Nonmalignant toxic effects of EDB inhalation included damage to the respiratory system, liver, kidney, testis, eye, and adrenal cortex. A dose-response was apparent for hepatic necrosis, toxic nephropathy, and testicular degeneration and atrophy. Testicular segeneration and atrophy were found in 2 out of 50 of the male controls, 12 out of the 50 low dose males, and 23 out of the 49 high dose males. Some of the cases of testicular atrophy may have been associated with testicular tumors and mesotheliomas rather than directly resulting from EDB exposure. The increase in numbers of testicular tumors was not statistically significant, as can be seen in Tables 1 and 2.

A chronic inhalation bioassay was conducted by NIOSH to evaluate the effect of disulfiram on carcinogenic and other toxic effects of EDB. (Ex 4–18) The findings have been reported in several publications (Ex. 4–18) Plotnick et al., 1979; Wong et al., 1982; Ex. 4–7). The study exposed four groups of 48 male and four groups of 48 female Sprague-Dawley rats to room air or 20 ppm EDB for 7 hours per day for 5 days per week over an 18 month period. Diets which contained 0.05% disulfiram were given to one set of controls and EDB exposed rats.

Rats were observed for clinical signs. Body weights were recorded weekly for the first 14 weeks and monthly thereafter. Both the EDB and disulfiram exposures reduced survival rates. A hematological examination was performed and a complete necropsy was performed on all rats, including gross and microscopic examination. Findings were statistically evaluated and are discussed in the Final Report (Ex. 4–18). The numbers of rats with tumors were as follows: 15 out of 96 controls on the diet, 13 out of 96 controls on the disulfiram diet, 54 out of 96 EDB exposed rats on the control diet, and 90 out of 96 EDB exposed rats on the disulfiram diet.

The report states its findings as follows: "Male rate receiving EDB exposure has significantly higher tumor incidences in spleen, adrenals and subcutaneous tissues than either the control or disulfiram tested rates. Also a significant finding was the high incidence of hemangiosarcoma in the spleen of male rate exposed to EDB. Tumors were also found in the liver, kidneys, and lungs in these animals * * * Female rats exposed to 20 ppm EDB also showed significantly high tumor incidences in the spleen (hemangiosarcoma), adrenals and mammary glands. Tumors were also found in the liver" (Ex. 4–18, p. 31).

In rats, the previous NCI/NTP study reported nasal tumor incidences of 0 out of 50, 39 out of 50 and 41 out of 50 for 0, 10 and 40 ppm in males and 1 out of 50, 34 out of 50 and 43 out of 50 for 0, 10, and 40 ppm in females. The presence of nasal tumors was not published in the original NIOSH publications. However, nasal tumor data from the study were made available to the reviewers for use in the EDB risk assessments. (SRI 1982, Ex.11)

When disulfiram was included in the diet, the toxicity of EDB was enhanced by every measurement in the study. Rats inhaling 20 ppm of EDB did not have increased incidence of testicular changes compared to controls; however, 90% of the male rats inhaling 20 ppm of EDB combined with 0.05% disulfiram in the diet developed testicular atrophy. These findings are summarized in the NIOSH report. (Ex. 4–18, Table 7)

In the NIOSH and NCI/NTP studies, four doses—0, 10, 20 and 40 ppm—were used for relatively long perious of time. The exposure duration for the 20 ppm groups. (NIOSH) was 18 months (78 weeks). For the NCI/NTP study at 10 ppm and 40 ppm the exposure duration ranged from 78 weeks to 103 weeks. The strain of rats in the two studies differed. Thus, two well-conducted inhalation studies demonstrated that EDB is a potent carcinogen not only in two strains of the same animal, but also in two different spacies at three different doses.

b. *Oral Administration Studies* NCI published this study in March 1976 as a final technical report entitled "Bioassay of 1,2-dibromoethane for possible carcinogenicity". (Ex. 4–17) The information had been released in preliminary reports (Olsen et al., 1973; Powers et al., 1975; NIOSH Criteria Document, 1977 and a Current Intelligence Bulletin on EDB, 1978). Osborne-Mendel rats and B6D3F1 mice were administered either of the does levels of EDB in corn oil by stomach tube 5 days per week and the responses were compared with two control groups, of which one received corn oil and the other had no treatment. Concentrations of 4% were used in the rat bioassay and 1–2% in the mouse bioassay.

Groups included 50 males and 50 females for each does and species. In addition, for each species, 20 animals of each sex were vehicle controls and 20 animals of each sex were untreated controls. Time weighted averages for the high and the low does groups were 41 and 38 mg/kg/day for male rats, 39 and 37 mg/kg/day for female rats, and 107 and 62 mg/kg/day for male and female mice, respectively.

Animal were weighed weekly for the first 10 weeks and monthly thereafter. Doses were administered five days per week according to most current body weight. All animals fo one sex received the same dose.

Survival rates and body weight changes in the rats indicated toxicity at both the high and low doese. These effects were apparent in males and females after 10 weeks. The toxic responses in the high does male and female rats led to the suspension of the dosing at week 17 for 13 weeks, and a reduction of the does to 40 mg/kg/day for the remainder of the study. The last weeks of the study used cyclic administration (four weeks of EDB alternated with one week of no dosing). The bioassay clearly utilized doses which exceeded the maximum tolerated does [MTD] and one-half MTD.

The results of this bioassay are tabulated in Exhibit 11, Table 11 C–4 p 67.

A statistically significant increase in squamous cell carcinomas of the forestomach were observed in male and female rats and in male and female mice dosed with EDB. The female rats also has statistically significant increases in hepatocellular carcinomas, while the male rats had nonsignificant increases in hepatic lesions. Hemangiosarcomas were dound in male and female rats and the incidences were statistically significant in the males. Male and female mice had statistically significant incidences of alveolar/bronchiolar adenomas.

Based on these findings, NCI concluded that EDB is an animal carcinogen. In addition, the International Agency for Research on Cancer (IARC) concluded in 1977 that EDB was carcinogenic to rats and mice, based solely on the NCI oral gavage study.

c. *Skin Painting Studies.* Van Duuren et al. (Ex. 4–19) included EDB in a chronic skin painting study in Ha:ICR Swiss mice. In the first experiment EDB was dissolved in acetone and 75 mg of it were painted once on the shaved backs of 30 mice. Starting 14 days later, 0.005 mg of a cancer promoting substance (phorbol myristate acetate) dissolved in acetone was painted on the same site 3 days per week. Two mice developed papillomas. These findings were not statistically significant when compared to controls.

In a second experiment two dose levels of EDB (50 mg and 25 mg) were

applied to the shaved backs of mice 3 days per week. There were 30 mice treated at each dose level. The increase in skin papillomas, carcinomas and lung tumors was statistically significant in the 50 mg group. Lung tumors were also significantly increased in the 25 mg group. The doses were estimated by SRI (1982) to be 1875 mg/kg in the 75mg/mouse; 1250 mg/kg in the 50 mg/mouse; and 625 mg/kg in the 25 mg/mouse. The "distant" tumors found in the lung indicate that EDB penetrates the skin and can produce tumors away from the site of application.

OSHA believes that the studies described above unequivocally demonstrate that EDB is a potent animal carcinogen. EDB when administered by either inhalation, dermal skin painting or oral gavage induces carcinogenic responses at multiple sites. Tumors were found at the site of exposure, i.e., the site at which the highest concentration would be expected. The "contact-site" tumors were specific for the dose route and tumors were not seen at that site when the route of exposure was changed. For example, the forestomach tumors found in gavage studies were not observed in the inhalation studies; nor were the nasal tumors that were found in the inhalation studies observed in the oral administration or the skin painting studies. Tumors were also found in remote sites in each of the four studies. Moreover, certain primary cell tumors were common to the inhalation, oral gavage and skin painting studies.

2. *Epidemiological Investigations.* Few epidemiological reports are available concerning the health status of persons exposed to EDB. Those that are available are considered inadequate for assessing the potential carcinogenic risk of EDB to humans due to a number of limitations in study design and analysis, such as: The number of workers studied was small; the data on EDB exposure was missing or incomplete; and often the time since first exposure to EDB was too short to observe possible long-term health effects.

In response to an OSHA Request for Information on EDB in 1978 (43 FR 11227–11229), both the Dow Chemical Company and Ethyl Corporation submitted reports of three studies which examined the frequency of death due to cancer among persons occupationally exposed to EDB (Ex. 2–23, 2–11). In addition, a study of 53 Ethyl workers was later submitted (Ex. 7–8). OSHA is not aware of any other studies which attempt to assess the risk of cancer among persons exposed to EDB.

In the first study, Ott and his colleagues investigated the mortality experience of workers employed in two Dow EDB manufacturing plants. The report of this study was published in 1980 (Ex. 4–20). Workers at one plant (Unit 1), located in Texas, were exposed primarily to EDB, bromine, ethylene, sulphur dioxide, and chlorine. Workers at the second plant (Unit 2), located in Michigan, were exposed to EDB, as well as a variety of other chemicals, including several recognized human carcinogens such as arsenic and benzene and several substances which are carcinogenic in animals such as vinyl bromide, carbon tetrachloride, and chloroform. The number of workers who died from specific causes of death was compared to the expected numbers of deaths from those causes. Expected numbers of deaths were derived from age-specific and calendar period-specific mortality rates for U.S. white males.

In Unit 1, a total of 99 employees were identified who had been employed at any time between 1942 and 1969. As of January 1, 1976, 21 of these workers had died. This number did not differ substantially from the number of deaths that would have been expected, 19.5, but neither did it indicate the "healthy worker effect" commonly observed in industrial populations. The "healthy worker effect" is the effect observed when comparing mortality rates in the general population, which includes both employed and unemployed persons, to those of an employed population, who by virtue of their ability to work would be healthier. Consequently, occupational cohorts typically have substantially less mortality compared to the general population.

Examination of deaths due to cancer revealed that two workers died from cancer compared to the 3.8 expected. However, the small number of workers included in this cohort limited the study's power to detect relatively moderate excesses in cancer mortality. Statistical power is the ability of a study to detect an excess risk of mortality if such a risk is truly present. Generally it is considered desirable for studies to have at least 80% power to detect the risk of a specific magnitude. OSHA calculated that the statistical power of this study to detect a 1.5-fold increase in all cancer deaths was 17.8%. A 1.5-fold increase would correspond to an excess risk of 50%. Thus, this study's power of 17.8% was highly inadequate for detection of an excess cancer risk of 50%. Since cancer is such a common cause of death in the U.S., OSHA calculates the power to detect increases in risk of 50% or greater. (See OSHA Technical Submission #1 and #2 for a description of how statistical power was calculated).

In Unit 2, 82 workers were identified who had been employed between 1940 and 1975. Seven malignancies were observed versus 2.8 deaths expected (p less than 0.05). Five workers from this cohort had also been exposed to arsenicals: two subsequently died from lung cancer. These two individuals had been exposed to arsenicals for 1.5 and 20 months respectively and to EDB for 102 and 111 months respectively. When the five workers exposed to arsenicals are included in the analysis, the lack of a "healthy worker effect" is noticeable. By January 1, 1976, the total number of workers who had died from all causes, 18, was slightly but not significantly greater than the 13.6 expected number of deaths. Of the seven deaths from malignancies, two were due to cancer of the digestive system, two were due to cancer of the respiratory system, and three were due to cancer of other sites. Both lung cancer deaths occurred in workers exposed to arsenicals as well as EDB.

When the five individuals who were also exposed to arsenicals were excluded from the analysis, a total of 15 deaths were observed compared to 13.0 expected. Five deaths from cancer were observed and 2.2 were expected (p less than 0.07). Excess numbers of deaths from non-malignant respiratory disease were observed in Unit 2 (3 observed versus 0.5 expected, p less than 0.05). This could indicate that EDB is associated with lung disease; however, the number of deaths from lung disease is too small to permit conclusions to be drawn.

Although the number of deaths due to cancer in Unit 2 appears to be somewhat elevated, a larger number of observations as well as a more detailed presentation by site and level of exposure would be needed before conclusions could be drawn about the cancer risk at this plant. This study had 11.7% statistical power to detect a 1.5-fold increase in cancer risk in Unit 2. For Units 1 and 2 combined, the statistical power was 25.9% to detect a 1.5-fold cancer risk.

Ott et al. (Ex. 4–20, p. 167) concluded: "The findings of this observational study need to be interpreted cautiously owing to the limitations in the size of the study population and the variety of toxic agents to which individuals in Unit 2 may have been exposed" * * * Findings of this investigation neither rule out nor establish EDB to be a human carcinogen.

The second and third studies were investigations of workers at two Associated Octel plants in Great Britain, by Turner and Barry. The results of

these two studies were published in 1979 (Ex. 7–10). In addition, Turner has furnished tables to OSHA which complete the follow-up of the workers at both plants through 1979 (Ex. 7–11). No information concerning exposure levels to EDB or other chemicals in either plant is available.

In the first plant (Factory B), located in Almwch, the vital status was determined for 273 workers with potential exposure to EDB who had been employed at any time between 1952 and 1975. Of these 273 workers, 36 were known to have died by the end of 1979. Eleven of these 36 workers had died from cancer. Turner and Barry concluded: "No evidence of any increase in the death rates from cancer could be detected."

The technique used to analyze the mortality experience at the Almwch plant is considered crude because it inadequately controlled for differences in cancer mortality by age and calendar time period. For example, the study cohort's mortality during 1954–1979 was compared to local mortality rates during 1975. Because cancer mortality rates have risen over time, this comparison would result in an underestimation of risk. In addition, this study is so small that it had low statistical power to detect excess cancer risk. Hence, this study's finding can be, at most, inconclusive.

In the second plant (Factory A), located in Hayle, an initial list was complied of 242 workers who had been employed during 1947 or later; some of these workers had been employed since 1940. Of these 242 workers, 84 were eliminated from the analysis due to insufficient information, and an additional 41 were dropped because they had been employed for fewer than 4 years. Of the remaining 177 workers, 39 had died between 1947 and 1979. Five of these deaths were due to cancer, including two deaths from cancer of the bronchus. The mortality of the study cohort during 1940–1979 as conpared to local population mortality rated during 1951 and 1970. The authors concluded that no excess cancer risk was observed at this plant.

As in the Almwch plant, the analysis of the Hayle plant inadequately controlled for differences in cancer mortality by age and calendar time period. Because of the methodologic limitations and the small number of workers included in this study, no conclusions can be drawn concerning the cancer risk at this plant.

The mortality of fifty-three Ethyl EDB production workers was studied in 1978 (Ex. 7–6). Their length of exposure to EDB ranged from 3 months to 10 years. Ethyl found EDB levels in various plants which ranged from "nondetected" to 4.5 ppm. Of 95 samples taken, 66 were below 0.15 ppm, 8 were between 0.5 and 1 ppm and 231 fell between 1.0 and 4.5 ppm. The one death in this group was from cancer of the kidney. This study is too small to contribute useful information on the human carcinogenicity of EDB.

In summary, OSHA believes that the currently available epidemiologic studies of workers exposed to EDB cannot unequivocally indict EDB as a human carcinogen. These studies are inadequate for this prupsoe due to small study populations, resulting in low statistical power to detect excess cancer risk. In addition, the studies by Turner and Barry failed to use standard epidemiologic techniques to control for changes in age-specific cancer mortality rates over time.

C. Reproductive Effects

The effect of EDB on male reproduction has been investigated in animals and humans. The animal studies clearly establish the potential for human reproductive toxicity. Although the human epidemiologic studies do not show an effect on reproduction, due to the methodologic limitations they do not rule out the possibility of EDB having an adverse effect on the human reproductive system.

1. *Human Studies.* In 1977, NIOSH (Ex. 7–7c) evaluated the reproductive health of EDB production workers at the Houston Chemical Company. Most the EDB production systems at this plant were entirely enclosed. The plant installed a new EDB unit in 1977 to replace a deteriorating unit. Of 25 personal breathing samples and 8 general area samples, EDB was detectable only in a single general area sample (0.88 mg/m ^{3} =0.115 ppm). Ethylene dichloride, another animal carcinogen, was detectable only in a single personal breathing sample(1 mg/m ^{3} =0.247 ppm). Company sampling data indicated that EDB exposures ranged from less that 1 to 53 mg/m ^{3} (less than 0.130 to 6.897 ppm) when the old EDB unit was in use.

According to the NIOSH Criteria Document for EDB published in 1977, the lower limit of detection for the described sampling and analytical method 0.0002 ppm. Hence, the levels of EDB exposure in the Houston Chemical Plant must have been extremely low in order to have escaped detection. In the one area where EDB was detected by the NIOSH survey, supplied-air respirators and gloves were required for workers.

NIOSH medical personnel evaluated 22 workers potentially exposed to EDB at the time of the survey, 2 workers with past exposure to the old EDB unit, and 9 non-exposed workers at the plant. No significant differences in testosterone levels, follicle stimulating hormone levels, and sperm density were observed in the exposed workers compared to the non-exposed workers. However, lutenizing hormone (LH) levels were significantly increased in EDB exposed workers compared to non-exposed workers (p less than 0.02).

LH is a pituitary gonadotropin that regulates testosterone production by Leydig cells in the testis. The elevated LH levels in the EDB workers may indicate that the Leydig cells require abnormal stimulation to produce the normal amount of testosterone. The data also indicated a difference in median sperm count between the exposed workers (54 million cells/ml) and the non-exposed workers (79 million cells/ml).

NIOSH concluded: "The available data indicates that there is a potential toxic effect of ethylene dibromide, as indicated by the LH levels; but there is no overall statistically significant effect on sperm count or evidence of testicular toxicity * * * It should be strongly emphasized * * * that this study on ethylene dibromide does show some signs of potential testicular toxicity and it should be treated as a toxic agent." (Ex. 7–7c, p. 10).

Dibromochloropropane (DBCP) is a chemical that is very similar in structure to EDB. DBCP caused a dramatic increase in sterility among exposed male workers. OSHA promulgated a standard for DBCP in 1978 based on its adverse reproductive effects. NIOSH suggested that the difference in findings between reproductive studies of workers exposed to dibromochloropropane (DBCP) and this study of EDB workers might be due to EDB acting by a different mechanism on the testis, or being a weaker toxic agent. The difference may be due to non-epidemiological reasons such as the very low exposures to EDB, or the small number of exposed workers studied.

OSHA calculated that this study had about 17% statistical power to detect a 1.5-fold risk of having a sperm count below 25 million cells/ml. This was based on the 11.1% of the non-exposed workers (1 of 9) that had a sperm count below 25 million cells/ml.

Dr. Richard Levine surveyed the reproductive experience of 102 EDB exposed workers employed in fumigating papaya or packing fumigated fruit (Ex. 5–36). The survey took place in

Hawaii in March 1981, and consisted of interviews to ascertain live births, miscarriages, stillbirths, and early infant deaths. Seventeen males and seven females had never been married and therefore were not included in the analysis. Levine also excluded the remaining 16 male employees because he deemed the small number of preemployment births for wives of male employees to be insufficient for analysis. About 94% of the 62 female employees included in the analysis had been packers; hence, their exposures to EDB were quite low.

Expected numbers of births were derived from national birth probabilities specific for maternal birth cohort, for age, parity, and race (white, all other). Standardized Fertility Ratios (SFR's) were computed by dividing the observed numbers of live births by the expected numbers of live births. Levine compared the SFR's for the preemployment and employment periods in order to determine whether EDB exposure had reduced fertility.

Levine et al. (1981) had previously tested this method by surveying fertility among DBCP workers, a high proportion of whom has severly depressed sperm counts (12 of 39 male workers). They concluded that the impaired fertility of the DBCP workers could have been detected by surveying live births. However, they characterized this study method as "not a sensitive indicator" for risk of infertility. Their survey indicated that fertility was reduced by 60% to 80% among workers exposed to DBCP. Statistical power to detect decreased fertility would have been greatly reduced if DBCP had been a less severe testicular toxin.

For married female workers with EDB exposure, the SFR was 1.71 compared to the combined SFR of 2.36 for married female workers prior to employment and married female workers with no EDB exposure. This difference between the two SFR's (equal to a 28 percent reduction in fertility) was not statistically significant. Unmarried female workers did not exhibit any reduction in fertility; however, the expected number of births for this group was small (0.5) and thus unstable. Because of the effect of employment status on female workers' fertility, it would have been preferable to compare the exposure employed group solely with the non-exposed employed group. Unfortunately, the expected number of births was small (2) and unstable among the non-exposed group of female workers.

Levine calculated the statistical power of his method to detect significant (p less than 0.05) decreases in fertility among married female workers. According to his calculations, this study had roughly 40% power to detect a 50% decrease in fertility. The study had roughly 80% power to detect a 70% decrease in fertility. Generally, a power of 80% or higher is considered desirable in order to lessen the probability of a failure to observe a true risk. Hence, EDB would have to exert an effect comparable to DBCP in order for this study to have sufficient statistical power. Commenting on his statistical power calculations, Levine stated: "Due to the small number of births expected during exposure, however, the analysis lacked the power to detect a mild or moderate effect" (Ex. 5-36, p. 8).

Levine compared the incidences of miscarriages, stillbirths, and early infant deaths per reported pregnancies during the preemployment period with the incidences during the employment period of the exposed and non-exposed workers. No clustering of these events was apparent in relationship to EDB exposure. This analysis had such a small number of pregnancies that the power to detect an increase in risk of these events was low.

Levine concluded that this study "has revealed no evidence of a severe decrease in fertility related to low-level exposure" and that "there was no indication of an abnormal aggregation of miscarriages, stillbirths, and early infant deaths with EDB exposure" (Ex. 5-31, p. 8).

Levine also surveyed the reproductive experience of employees of Ethyl Corporation at the EDB production plant in Magnolia, Arkansas (Exhibits 5-31D, 5-36). This survey took place in April 1981 and initially included 184 employees who were interviewed concerning their reproductive history. Subsequently, Levine excluded from the analysis 6 female employees, 10 never-married male employees, and 12 male employees who had previously worked at other chemical plants. Levine used the same method of analysis for this study as for his study of the Hawaiian papaya workers. Standardized Fertility Ratios (SFR's) were calculated for preemployment and employment periods for all males. Exposures were estimated by duration of exposure and intensity assigned to each job title.

Fertility of male employees exposed to EDB was not reduced relative to male employees not exposed to EDB. The ratio of SFR's for exposed workers to non-exposed workers was 1.25, with 90% confidence limits of 0.85-1.78. Hence, there is a 90% chance that the true fertility of EDB exposed workers in this study is not reduced by more than 15% compared to non-exposed workers. However, the nonexposed category included preemployment fertility which may have been reduced because of marital status. Thus, if the exposed employees' fertility were reduced it may not have been observed in this analysis.

When the married male workers were classified by intensity of exposure, no gradient of reduced fertility with increasing exposure was apparent, except in the greater than 3 year exposure category. Levine felt that because this reduction was not statistically significant and was uniformly distributed between low and high intensity jobs, it could not be related to exposure duration. However, Levine had already stated that small numbers of expected births precluded valid inferences about the possible effects of chemical exposure for the categories "none," "EDB/VB," and "area 1" used in the study.

Levine concluded that this study "revealed no evidence for a decrease in fertility related to exposure to ethylene dibromide, vinyl bromide, or a multiplicity of chemicals which may include ethylene dibromide and vinyl bromide" (Ex. 5-31D, p. 7). Also, Levine found no evidence for an association between chemical exposure and miscarriages, stillbirths, neonatal deaths or birth defects.

Dr. James Dobbins of the University of Texas critiqued the studies of Dr. Richard Levine (Ex. 5-55). He disagreed with Levine's conclusion that EDB does not lead to a severe decrease in fertility, stating that "occupational exposure to EDB could have a strong effect on fertility and still produce the results obtained by Levine" (Ex. 5-55, p.1). Dobbins enumerated the following disadvantages of Levine's use of SFR's:

(1) The expected fertility rates for women are dependent on their observed fertility (parity). If a woman's fertility has been reduced by chemical exposure, her expected fertility also will have been held artificially low. Hence, the expected fertility "will depend on and always be close to observed fertility"(Ex. 5-55, p.5). This would result in underestimation of risk of reduced fertility.

(2) Differences between high fertility and low fertility populations are greater at older ages. Because workers are younger during the period preceding employment, a high fertility occupational cohort would have a pre-exposure fertility close to expectation. For a high fertility occupational cohort an employment period SFR would be based on an underestimate of expected fertility and hence comparing preemployment and employment period

SFR's would result in an underestimate of risk.

(3) The SFR's of married female workers are derived from the national birth probabilities for both married and unmarried women. Because women who are married have higher birth rates, expected fertility is underestimated by this procedure. Also, fewer women workers were married during the preemployment period and employed women tend to have lower fertility than unemployed women. Comparisons between preemployment periods and employment periods are problematic because of underestimates expected fertility.

(4) The SFR methodology has low statistical power because few women (or men) have been exposed exclusive to any single chemical and because total fertility in the U.S. is now less than 2 children per woman. Dobbins stated that fertility impairments of the magnitude of that related to DBCP rarely occur.

Regarding the study of Hawaiian papaya packers, Dobbins commented that most of the studied women were Asian and that Hawaiian Asians have higher fertility than U.S. whites. Hence, using U.S. birth probabilities would underestimate expected fertility. Dobbins also did not agree with Levine's basis for excluding males from the study: insufficient numbers of births for analysis among males. Dobbins pointed out that the small number of births for male employees may have been due to EDB exposure. In addition, Dobbins was concerned that including women who were only potentially exposed to EDB would result in underestimation of risk.

Another problem mentioned by Dobbins was the low statistical power of the study, which was exacerbated by use of a two-tailed test of significance. Dobbins stated that the employment SFR would have to decline 69% in order to detect a statistically significant decrease in fertility. Dobbins also believed that it was inconsistent of Levine to draw conclusions about unmarried employment period SFR's which were dervied from very low expected values (0.54), after stating that SFR's with expected values less than 3.0 were "insufficient for analysis." Dobbins also criticized Levine for combining fetal losses, stillbirths, and infant deaths in one measure of adverse reproductive outcome, uncontrolled for maternal age and other pertinent variables. Dobbins described Levine's findings for the Hawaiian papaya packers:

> There is evidence of a decline in fertility associated with potential low-level exposure to EDB, but this decline is not statistically significant because of small sample size, low post-exposure fertility, and conservative methodology (Ex. 5–55, p. 14).

Concerning the study of Ethyl Corporation employees in Magnolia, Arkansas, Dobbins stated that the study had the following problems: small sample size; poor measures of exposure, inclusion of minimally exposed persons in the sample, and use of a two-tailed test of significance. Dobbins stated:

> In spite of a number of conservative biases in this study, especially small sample size and slight or unknown levels of exposure, there was some evidence of reproductive impairment due to exposure to EDB. Many of the results were equivocal and the study is clearly not an indictment of EDB. On the other hand, these results cannot be used in any way to exonerate EDB (Ex. 5–55, p. 17).

OSHA believes that there are a number of difficulties with the Levine studies which limit the extent to which th ir findings can be generalized to EDB-exposed populations. Choosing an appropriate comparison group that closely resembles the study group is crucial. National birth probabilities may not be appropriate for purposes of comparison with small local populations. Another problem when studying male workers is that they are, in a sense, proxy respondents for their wives. This could lead to under reporting of miscarriages and stillbirths. Yet another problem is that studies of birtns need quite a large cohort to detect toxic effects on the reproductive system, if those toxic effects are not as catastrophic as those of DBCP. Poorly defined exposure histories add further to the difficulties in the study's interpretation.

A reproductive study was conducted by Ter Haar (1980) among Ethyl Corporation workers. Fifty-nine sperm samples were collected in 1977, and 24 in a follow-up study in 1978. The author reported that the sperm counts compared favorably with published levels in the general population. The counts in workers with exposures below 0.5 ppm were compared with counts in workers with exposures between 0.5 and 5 ppm. Forty workers had exposures of less than 0.5 ppm and 19 had exposures in the higher range. The apparent trend towards lower sperm counts in the 0.5 to 5 ppm range was not considered significant by the authors. Ter Haar did not specify the protocol followed in obtaining and processing the specimens. Furthermore, no concurrent comparison group was sampled, which precludes discovery of any artifacts from laboratory practices. Because of its methodological limitations, this study should be considered only as an observational report.

Wong et al., 1979 conducted a retrospective study of fertility among men exposed to EDB at four U.S. production plants (Ethyl, Dow, Great Lakes and Houston Chemical). The authors used reproductive histories of the workers' wives as a surrogate measure of male fertility. The numbers of live births to the wives of exposed workers were compared to expected numbers derived from national fertility rates for women adjusted for maternal age, parity, race, and calendar year. Standardized birth ratios were calculated dividing the observed number of births for the married male workers by the expected number of live births. A total of 297 couples with 1092 person-years of observation were included in the study.

For three of the plants (Ethyl, Dow, Great Lakes), the plant-specific standardized birth ratios of the workers were close to unity (i.e. were not significantly higher or lower than national fertility rates). One plant's (Houston Chemical) standardized birth ratio was significantly decreased compared to the national fertility rates (11 births observed, 22.2 births expected, p less than 0.05). No exposure data were available for this plant.

Wong et al. characterized reproductive performance of wives as a measure that could provide "only a limited assessment of the exposed worker's fertility," (p. 99) mentioning that "reproduction performance is determined by a complex interaction of volitional and biological variables * * *" (p. 101) The authors reported that the average exposure level to EDB was not higher at the plant with decreased live births (Houston Chemical) compared to the other plants, so that the decreased births could not be attributed to differences in exposure levels. The authors pointed out that about 33% of the couples from the Houston Chemical plant had a sterilized partner compared to 30% of couples in a national survey conducted in 1976.

For all four plants combined, the statistical power to detect a 20% decrease in fertility was reported by Wong et al. to be 90%. This power calculation might not be correct. OSHA calculated a power of 60% to detect a decrease of this magnitude. Moreover, the power of the study as determined by the authors did not exclude person years of exposure during pregnancy or surgically sterilized workers. Other factors which limit interpretation of Wong et al.'s study findings include lack of consideration of other reproductive indicators (miscarriages and stillbirths), potential differences in birth rates

between the regions in which the plants were located and the U.S. as a whole, ethnic differences in plant populations which could affect the rates, and difficulty in deriving expected numbers from both married and unmarried persons for comparison with married persons. Finally, the exposure categories chosen seem unbalanced, with no intermediate level, and no explanation by the authors of their reasons for choosing these categories.

Equitable Environmental Health (1977), Inc. studied a British EDB production plant. The authors compared live births for 41 married workers with either occasional, regular or irregular exposures to EDB in the workplace to the live births for 41 married workers who were not exposed to EDB. EDB exposure levels were not reported. The birth rates were adjusted for parity and age of the father. EDB exposed workers did not have lower birth rates than non-EDB workers. Interpretation of this study is hampered by the very small sample size, incomplete exposure determinations, general limitations of using live births to assess fertility, and the unexplained and unusual adjustment for paternal rather than maternal age.

2. *Animal Studies.* Reproductive toxicity of EDB has been studied in rats, mice, chickens, rams and bovine bulls. These studies were summarized by NIOSH in 1977 and reviewed by Rannug in 1980. Those studies which are appropriate for quantitative analysis of dose response relationships will be discussed. An overview of the research on reproduction is also provided for reference.

In 1955, Bondi et al. showed that in hens fed grain which had been fumigated with EDB the weight of eggs and egg production rates were reduced. EDB concentrations on the grain ranged between 50–60 and 270–320 ppm. When hens were given EDB in total feed ranging from 10 to 30 ppm, EDB levels of 10 ppm. in total feed produced egg-weight reductions by the eighth week. The effects were reversible for hens that laid smaller eggs and did not cease laying eggs. Alumot et al. (1968) reported that feeding of EDB fumigated mash to chicks reduced egg size and number of eggs but did not affect onset of egg production. The chicks were exposed from 1 day of age, fed diets with 40 ppm EDB or control feed, and growth parameters were measured.

In another experiment, 1 year old laying hens were exposed to 100 ppm EDB in feed and the fertilization rates measured. EDB reduced the number of eggs and the fertilization rates. Male chicks, 3 days old, were fed 0, 80 and 160 ppm EDB in the diet and growth parameters and reproduction parameters were measured at 3 months. Sexual development was not affected by EDB in those male chicks. Fertility was also measured in mature cockerels fed 150 and 300 ppm EDB in diets for 2, 4, 8 or 10 weeks. These males' fertility was not affected by EDB.

Based on this series of studies, it was concluded that EDB in diets would reduce growth rate and egg production but would not alter the onset of egg laying in hens or sperm production in male chickens. Other studies (Rannug, 1980) demonstrated that EDB did not alter follicle stimulating hormone (FSH) production and that the EDB effects were not altered by injection of pituitary extract. These studies show that EDB has effects on reproduction in female chickens and that the effects are specific to the reproductive system rather than the result of generalized systemic morbidity. A difference in uptake of radio-labelled albumin and globulins into the egg yolk and ovarian follicles was shown in EDB treated hens. Due to the biologic differences between human reproduction and fowl reproduction, these studies have a somewhat limited utility for analyzing human reproductive risk.

A series of male reproductive studies were carried out in bulls (Amir and Volcani, 1965; 1967; Amir, 1973, 1975; Amir and Lavon, 1976; Amir et al., 1977; NIOSH, 1977; Rannug, 1980). These studies demonstrated toxic effects of EDB on spermatogenesis. Reproductive impairment, as measured by decreased sperm density and motility and sperm abnormalities, was found after two or more weeks of exposure to 2 or 4 mg/kg EDB in the diet. Studies in 1973 and 1977 by Amir and colleagues investigated the mode of reproductive toxicity in bulls given EDB. The authors concluded that the actions of EDB occur in the testes affecting the spermatogenesis and sperm maturation. Spermatozoa with deformed heads and tails were produced. Deoxyribonucleic acid (DNA), amino acid and lipoprotein changes were also reported in spermatozoa.

Eljack and Hrudka (1979) reported dose response data on the effects of EDB on the sperm of 18 Columbia rams. Four controls were studied. Subcutaneous doses in olive oil of 7.8, 9.6 and 13.5 mg/kg/day of EDB were administered for 12 days so only the preceding lower doses were used. Systemic reactions were seen at 16.9 mg/kg/day therefore only the three lower doses were used. Sperm morphology and motility were determined. Normal findings were seen over the two exposure weeks and for three weeks thereafter. Declines in sperm motility began to be observed at five weeks and were greatest between 9 to 12 weeks. Sperm had returned to normal by week 15.

A mitochondrial "marker" enzyme was also altered. Mitochondrial sheaths were altered, acrosomes were abnormal, and extensive nuclear abnormalities were seen. The effects were dose related and significant at the 7.8 mg/kg/day dose. The four weeks delay in onset of effects suggest that EDB's actions at these dose levels occur primarily in the meiosis and multiplication stage rather than acting directly on the differentiating sperm organelles. These findings are consistent with an action on DNA synthesis and suggest that EDB is a chemical mutagen, according to the authors.

Edwards, Jackson and Jones, (1970) studied reproductive effects in male Wistar rats and male RF/Hirak mice. Five daily doses of 50 mg/kg of EDB injected intraperitoneal (IP) reduced average litter sizes from matings which occurred 3 to 4 weeks after dosing. This suggests an action on spermatids. The isolated metabolite S-(2-hydroxyethyl)-cysteine has no effect on mouse fertility. Thus, EDB or an alkylating metabolite is responsible for the diminished fertility effects Tissue distribution of the labelled molecule of EDB was measured in mice. At one hour and 24 hours there was 3.1 and 0.66 per cent and 1.1 and 0.23 percent of the administered dose in the cauda epididymis and testes respectively. The highest concentrations of EDB were found in the small intestine at 1 hour (34%), in the large intestine at 3 hours (15%) and in whole blood at 24 hours (6.2%). IP administration at a dose level of 40 mg/kg was used in this experiment. Only 5% of the dose was excreted in the bile. If in fact EDB conjugates to glutathione in the liver, a higher percentage of EDB should be seen in the bile. Since only 54% was excreted this may mean either the EDB conjugates formed in the liver are not excreted in the bile or that they are formed in non hepatic tissue and are not available for biliary excretion.

Short et al. (1979) studied the effect of inhalation of EDB on reproduction in Charles River (CD) rats. Males were exposed by inhalation to 0, 19, 39 or 89 ppm EDB 7 hours per day, 5 days per week for 10 weeks. The rate of reproduction, fertility, mortality and morbidity were measured. The effects of EDB were dose related. Rats exposed to 0 and 19 ppm had normal weight gain and food consumption. At 39 ppm body weight gains were reducted (443 grams vs. 484 grams at exposure week 10) while decreases in both body weight

and food consumption occurred at the 89 ppm level. A high mortality rate (7 out of 33) was also observed in male rats exposed to 89 ppm.

In a female reproduction study, groups of 20 females were exposed for 21 days to 0, 20, 39 or 80 ppm EDB for 7 hours per day 7 days a week. Rats at the 80 ppm group did not cycle normally for 3 or 4 days after exposure. The rats were placed with proven males for a 10 day period. All females became pregnant with normal appearing uterine contents based on total implants, viable implants and resorptions. For females, body weight was reducted at 80 ppm but not at 20 and 39 ppm. A high mortality rate (10 out of 50) was seen at 80 ppm.

Male reproductive performance was completely blocked at the 89 ppm dose, but all males exposed to lower doses (0, 19 and 39 ppm) did impregnate at least one female rat. Estrus of the high dose female rats were adversely affected. The females had normal numbes of viable implants and resorptions. Severe teticular atrophy and reduced serum testosterone concentrations were observed at the highest dose (89 ppm) but not at 19 or 39 ppm. Atrophy of the epididymis, prostate and seminal vesicles was also found in the 89 ppm group on histopathology. In addition, prostatities and sperm granuloma occurred in high dose males. Some prostatitis also occurred in the lower exposure groups.

Biochemical paramenters were measured in the serum, liver and testes in male rats administered 0, 10 or 100 mg/kg EDB orally. No differences were fund in SGPT, SGOT, or BUN, two, four, or 24 hours after dosing. Non-protein sulfhydryl (NPS) activity was depressed (67% of the control value) in the liver at 2 hours, but was not changed in the testis. The four and 24 hour values are the same as control. The tissue distribution was measured after oral administration of 10 or 100 mg/kg EDB which contained C^{14}. Four hours after administration, the concentration in tissues from 3 rats were highest in the stomach and kidney, and lowest in the testis at both dose levels. The deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and protein varied in relative content of labelled C^{14}, but DNA was highly labeled in the testis.

This study (Short, 1979) show that inhalation of 80 ppm EDB in the air for extensive periods (7 hours per day for 5 or 7 days per week) produces severe toxicity in male and female rats, including adverse effects on survival, body weight, food consumption, and reproduction. The test is is a target organ. The effects are dose related with little change in reproductive function at 20 or 39 ppm concentrations. For males or females, C^{14} labelled EDB is clearly bound at 4 hours to DNA, RNA protein in the liver, kidney, testes (lowest in testes), and stomach which suggests potential for an action on the organs.

The previous findings in the male reproduction study (Short, 1979) indicate that 19 and 39 ppm exposures did not produce dominant lethal mutations. Teramoto et al. (1980) conducted a dominant lethal study for EDB and DBCP in rats and mice. No effect was produced by 10 or 30 mg/kg of EDB orally for rats or 100 or 150 mg/kg EDB for mice. DBCP and a control mutagen were positive in the same study. This is a well conducted study which shows that EDB may be weakly mutagenic *in vivo*. Edwards and Jackson (1970) investigated several metabolic and toxicologic aspects of EDB in mice and rats. The fertility studies used serial mating. EDB (50 mg/kg given to make rats and mice as a cumulative dose over 5 successive days by IP) produced a significant decrease in litter size in rats mated the third and fourth week after dosing but no differences were found in weeks one and two or weeks five through 10. In a comparable experiment, oral administration of 1 mg/kg of the EDB metabolite produced no effect on male mouse fertility.

Short et al (1978) studies teratogenic and embryotoxic effects of EDB inhalation during gestation in mice and rats. Charles River (CD) rats and CD-1 mice were used. Groups consisted of 15 to 17 rats and were divided into feed restricted and free access food groups. Starting at day 6, animals were exposed for 10 days to 20, 38 and 80 ppm EDB for 23 hours a day. Body weights, food consumption and survival were measured. Rats or mice were sacrificed on day 20 or 18 respectively. Fetuses were examined for skeletal and soft tissue anomalies by standard techniques.

One control group with food intake restricted to levels comparable to the food consumption of the 80 ppm groups was examined. Maternal food consumption and maternal and fetal body weights were reduced at 38 and 80 ppm. Reproductive changes were seen only at 80 pm. Deaths only occurred at 80 ppm. Dams exposed to 80 ppm had a reduced number of implants and no viable fetuses. The high percentage of resorptions in the 80 ppm group was evidence of considerable embryotoxicity.

The findings in treated mice were comparable to those of the rats. Groups of 18 to 20 were exposed to 0, 20, 38 and 80 ppm. Maternal food consumption and maternal and fetal body weights were reduced at 20 and 38 ppm dose levels. All animals in the 80 ppm group died. In the 38 ppm group, resorptions were increased and viable fetuses were decreased. The 20 ppm group also had an increased number of resorptions. These effects were embryotoxic but not necessarily teratogenic since changes occurred in food consumption and weight gains in the mothers. The increase in frequency of low body weight pups (runts) at 38 ppm in mice would not be considered a teratogenic response. The findings suggest a delay in fetal development with EDB treatment which would also be secondary to maternal effects.

While there are no reliable human data available to help assess the human reproductive effects of EDB, the available animal data clearly indicate that EDB causes adverse reproductive effects in the bull, rat and hen. In the absence of adequate human data OSHA feels it prudent and reasonable to assume that man is at least as sensitive as the most sensitive species for which data are available. Therefore, OSHA believes that several studies demonstrate that EDB could adversely affect mammalian reproductive development by interfering with the production of male gametes and the development of embryos.

D. Mutagenesis and Cytogenetic Effects

Mutation studies utilize techniques which measure specific aspects of the interaction between chemical compounds and cellular DNA. The five techniques defined below are utilized to measure mutagenic potential which is considered by some to be an indicator of carcinogenic potential. they are considered indicators because they demonstrate the test chemical's effect on DNA.

1. *Ames Assay*—The action of a chemical on cellular DNA (genetic code) is measured in a bacteria (*Salmonella typhimurum*). Mutagenesis is show when the chemical alters the DNA such that the strain of bacteria is transformed and acquires the ability to grow on a histidine deficient media. The number of colonies which grow is proportional to the potency of the chemical's interaction with DNA.

2. *Host-Mediated Assay*—Certain chemicals do not themselves act on DNA but are changed (metabolized) in the body to chemicals (metabolites) which can act on DNA. The host-mediated assay measures the formation of metabolites in rats or mice that act on DNA. In this assay the chemical and the indicator bacteria are injected together

into the peritoneum of the animal (host). After a period of time the bacteria are removed and its growth measured on the appropriate media. Transformed cells grow to form colonies; non-affected cells do not grow.

3. *Polymerase Assay*—This is a direct measure of damage to nuclear DNA from chemical exposure. When the DNA is damaged due to chemical interactions the injury is repaired by an enzyme known as DNA polymerase. The more chemical damage to the DNA, the greater the increase in activity. This test is more of a general measure of the test chemical's effects on DNA than the bacterial tests because it will measure nonspecific damage to the DNA.

4. *Dominant Lethal Mutation Assay*—When the damage to DNA is sufficient to produce a change in a gene's expression, a mutation occurs. Changes in genes critical to survival are lethal. When dominant genes are mutated by a chemical, the change may be lethal to the organism. This is a highly significant biological event and it is non-ambiguous. In the dominant lethal test male rats are exposed to the test chemical and then mated with normal females. Live births are counted and compared to the number of corporea lutea (measure of eggs released from ovary). The difference between live births and corporea lutea is related to lethal mutations.

5. *Deletion Mutation Assay*—Two types of mutations (changes in DNA are possible: A change in chemical components of DNA which alters the genetic code, and the deletion of parts of DNA which also alters the code. A deletion mutation assay is only a measure of the loss of parts of the genetic code.

The mutagenic effects of EDB have been reviewed in detail by NIOSH (1977), Rannug (1980) and IARC (1977). Mutagenic actions have been detected in a variety of *in vitro* and *in vivo* systems. A direct mutagenic action has been found using *Salmonella typhimurium* by Ames in 1971, Buselmair in 1972 and 1973, Brem in 1974, and McCann in 1975. EDB was also positive in the host-mediated assay in mice, with *S. typhimurium* G46. Using the polymerase assay unscheduled DNA repair was increased in opossum lymphocytes; and DNA damage was shown in mouse lymphoma cells at the thymidine Kinase Locus. *Drosophila melanogaster* studies showed an increase in x-chromosomal recessive lethal mutations for two consecutive breedings. Thus, EDB is a direct-acting mutagen based on a wide variety of tests.

Chemicals can produce deletion mutations without direct alkylation of the DNA resulting in mutagenic responses that are unlikely to predict cancer. In contrast, EDB was shown to produce mutations but not to produce deletion mutations. This suggests that the mutagenic responses of EDB could be predictive of carcinogenic interaction.

A specificity for EDB's mutagenic action is suggested by those tests which were not positive. They include the absence of deletion mutations in *S. typhimurium* shown by Alper and Ames in 1975 the absence of mutation with *Serratia marcescens* absence of chromosomal breaks in *Allium* roots or cultured human lymphocytes, and absence of dominant lethal mutation in mice after IP or oral administration. Further, there is evidence that EDB alkylates DNA but does not produce cross linking of DNA. This is consistent with the conclusion of relative specificity in the action of EDB on DNA. In other words, EDB tested positively in tests which weigh changes in DNA, not in tests which evaluate cross linking in the DNA. This suggests a metabolite of EDB is acting on the DNA rather than the EDB molecule itself.

Direct acting mutagens may also be metabolized *in vivo* to chemical species of greater mutagenic action. EDB is such a compound. Activation of metabolites is tested by adding liver enzyme preparation (referred to as "S9") to the Ames test system. A slight increase in the number of reversions was produced in the Ames system with TA1535, but the action was not dependent on the presence of the nucleotide energy source, NADPH, and was subsequently shown to be produced by soluble rather than membrane-bound enzymes. (Rannug, 1980) This observation sets EDB apart from other mutagens which are activated by S9. EDB was also "activated" to higher mutagenic activity by extracts of certain plants and by liver perfusion procedures which yielded highly mutagenic bile when EDB was added to the perfusion fluid. Thus the genotoxicity of EDB is complex. It is a direct acting mutagen and it is metabolized to one or more highly mutagenic compounds.

Van Bladeren et al. (1981) determined the relative effects of glutathione conjugation on the mutagenicity of a series of vicinal dihalogen compounds. They found that rat liver glutathion transferase activity towards EDB was relatively high compared to the other vicinal dihalogen strates tested. Thus, the glutathione conjugate is a predominant metabolite. The EDB-glutathione conjugate was highly mutagenic in the Ames test and in fact is much more mutagenic than EDB itself. This study shows that at least one of the metabolites of EDB, the glutathione conjugate, can increase the genotoxic potential of EDB. Further, since the distribution of EDB and GSH (glutathione) conjugate may differ *in vivo* it is possible that the target organs for the two mutagenic species may differ with one responsible for contact tumors and the other responsible for tumors in remote organs.

Elliott and Ashby (1980) used a mutagenic approach to show the synergistic response of EDB and disulfiram. Their observation is consistent with the increase in carcinogenic response seen in the rat study with disulfiram. This may suggest that specific precautions should be taken in cases where EDB exposures occur concurrently with other chemicals (e.g. pesticides) which act in the same manner as disulfiram.

Predicting the potential of a compound to induce mutagenic effects in humans is more difficult than predicting other types of toxicities, but the logic can still be founded on establishing the mechanism in appropriate non-human species. Valid studies demonstrating mutagenic effects in experimental animals, the mechanisms of those coupled with serious consideration of pharmacologic principles and biodistribution in humans, do establish the framework for presuming a mutagenic hazard to humans. OSHA therefore believes that the evidence of EDB's mutagenic potential in non-human species can be used to predict mutagenic potential for humans.

TABLE 1.—RESULTS OF THE NTP/NCI INHALATION BIOASSAY OF EDB IN FISHER 344 RATS—TUMOR INCIDENCE BY SITE

Tumor	Control	10 ppm	40 ppm
1. Nasal cavity:			
Adenocarcinoma (M)	0/50	***20/50	***28/50
Adenocarcinoma (F)	0/50	***20/50	***29/50
Carcinoma (M)	0/50	0/50	***21/50
Carcinoma (F)	0/50	0/50	***25/50
Adenomatous polyps (M)	0/50	***18/50	*5/50
Adenomatous polyps (F)	0/50	*5/50	*5/50
Adenomas (M)	0/50	***11/50	0/50
Adenomas (F)	0/50	***11/50	3/50
Squamous cell carcinoma (M)	0/50	3/50	3/50
Squamous cell carcinoma (F)	1/50	10/50	5/50
2. Lung:			
Alveolar/bronchiolar carcinomas or adenomas (F)	0/50	0/46	+5/47
3. Tunica vaginalis: Mesothelioma (M)	1/50	**8/50	***25/50
4. Mammary fibroadenomas (F)	4/50	***29/50	***24/50
5. Circulatory system:			
Hemangiosarcomas (M)	0/50	1/50	***15/50
Hemangiosarcomas (F)	0/50	0/50	*5/50
6. Pituitary adenomas (M)	0/45	++7/46	2/47
Pituitary adenomas (F)	1/50	***18/49	4/46

***p=0.001. **p=0.015. *p=0.028.
++p=0.006. +p=0.024.

TABLE 2.—RESULTS OF NTP/NCI INHALATION BIOASSAY OF EDB IN B6C3F1 MICE—TUMOR INCIDENCE BY SITE

Tumor	Control	10 ppm	40 ppm
1. Lung:			
Alveolar/bronchiolar adenoma or carcinoma (M)	0/41	3/48	***23/46
Alveolar/bronchiolar adenoma or carcinoma (F)	4/49	**11/48	***41/50
2. Circulatory system: Hemangioma or hemangiosarcoma (M)	0/45	0/50	4/50
Hemangioma or hemangiosarcoma (F)	0/50	***12/50	***27/50
3. Subcutaneous tissue fibrosarcoma (F)	0/50	+ + 5/50	***11/50
4. Mammary gland adenocarcinoma (F)	2/50	***14/50	+ 6/50
5. Nasal cavity carcinoma or adenoma (F)	0/50	0/50	**8/50

***p=0.001. **p=0.003. *p=0.046.
+ +p=0.028. +p=0.046.

E. Conclusions

Based on the discussion of the scientific evidence presented here OSHA believes that EDB is a potent animal carcinogen. EDB produces tumors at the site of direct contact and at sites remote from the site of administration. EDB and two of the principle metabolites (bromoacetaldehyde and N-acetyl cysteine) are positive in the Ames Salmonella assay. They are also positive in other *in vitro* systems with and without activating enzymes.

Pharmacokinetic studies discussed in Brown's risk assessment show that EDB is rapidly absorbed, metabolized by liver mixed-function oxidase enzymes and excreted in the feces and/or urine. The biological half-life of EDB in animals is about 1 day.

Target site of "direct" tumors are dependent on route of exposures. Oral doses of 20 and 40 mg/kg/day produced forestomach tumors. Inhalation doses of 10 and 40 ppm 6 hours per day produced nasal cavity tumors. Doses of 15 mg/mouse/day produced nasal cavity tumors. Doses of 25 mg/mouse/day applied to the skin of mice produces skin papillomas and carcinomas.

Tumors are produced at tissue sites remote from the site of contact in each bioassay. These included respiratory tract (lung) tumors in mice in the skin painting study; hemangiosarcomas of the circulatory system in rats in the inhalation studies, and alveolar/bronchiolar carcinomas in the mice in the inhalation studies. In the oral gavage study, hemangiosarcomas were also produced in the circulatory system.

The tissues remote from the site of direct contact in which tumors were produced would have had relatively low exposures to EDB. They presumably responded because of unique pharmacokinetic, metabolic or other biochemical characteristics. These sites are therefore of concern with chronic low level exposures. Mode of action studies have demonstrated the presence of EDB or a metabolite covalently bound in tissues.

Increased incidences of cancer have not been demonstrated by epidemiology studies on workers exposed to EDB in the chemical industry. The studies are of limited value because small numbers of workers were studied, limited exposure information relative to EDB was available and exposures to a variety of other possibly toxic chemicals occurred. While the absence of tumors in the studies is noteable, the studies do not rule out the possibility of low level indices of cancer in the workers.

Reproductive effects of EDB in several animal species have been clearly established. EDB's action, specifically in early stages of sperm development, has been shown. Doses as low as 80 ppm produced reproductive toxicity in male rats. The teratology studies showed malformations at doses which produced maternal toxicity. Malformations and anomalies were produced in rats and mice. These included: Runts, skeletal anomalies such as an enlarged occipital, fontanel and ossification effects which are consistent with delayed development. Based on this, it was conclused the EDB is not a potent teratogen.

Epidemiology studies on the reproductive effects of EDB are equivocal. Only one of the groups showed a decrease in family size but the effects were not dose-related. Further, the reduction in sperm counts with EDB were not statistically significant. This study shows that EDB's effects on male reproduction were marginal, if present at all, at the levels of exposures in these workers.

OSHA believes that the total risk to the health of employees exposed to EDB is the result of the compounded risks from carcinogenicity, mutagenicity, spermatotoxicity, teratogenicity, and damage to the kidneys, liver, spleen, respiratory tract, central nervous system, circulatory system, skin and eyes.

Therefore, the totality of the adverse health effects associated with exposure to EDB warrant the reduction in the PEL to 0.10 parts per million.

IV. Quantitative Risk Assessment for EDB

A. Introduction

Brown (Ex. 11) provided a succinct explanation of the rationale and basis for quantitative risk assessment. It is presented here as introduction.

There are several approaches to the estimation of risk to low exposures to airborne compounds. Mathematical models attempt to fit curves to data points observed at different exposure levels and from these curves to predict the risk at other, usually lower, exposures. These curves range from linear extrapolations to zero exposure and zero risk to curves which may deviate far from linearity at extreme doses. The use of a particular model or curve can be justified in part by statistical measure of "fit" to available data points. These considerations have been reviewed from the statistical standpoint. (Krewski and Van Ryzin, 1981).

In all cases it is assumed that the mathematical curves are reflective of biological processes that control the biological fate and action of the toxic compound. To date, these factors have not been quantitatively linked to the mathematical models. Biological factors which may play important roles in the risk assessment are (1) dose of the material at the sensitive tissue; (2) the sensitive tissue(s) itself; (3) the nature of the response(s); (4) rates and sites of biotransformation; (5) toxicity of metabolites; (6) chronicity of the compound (cumulative nature of the material or its actions); (7) pharmacokinetic distribution of the material (especially effects of dose on the distribution); (8) the effect of biological variables such as age, sex, species and strain of test animal; (9) and the manner and method of dosing the test animals.

It is clear that all of these factors cannot be easily incorporated into a single mathematical model. Therefore, selection of the data for evaluation in the model is an important factor in the risk assessment. In cases where several data sets are available, such as EDB, and the agent has a variety of actions, also true of EDB, the results of different approaches should provide a guide as to the optimal approach to risk assessment, and they should compare logically with each other (pg. 98–99).

In order to quantify the potential risk of cancer to workers exposed to ethylene dibromide, OSHA has reviewed several quantitative risk assessments submitted in response to the ANPR. Predictions based on both human data and extrapolations from other species, and several different mathematical approaches were considered.

OSHA and others examined several possible exposure scenarios for lifetime occupational exposure including TWA exposures ranging from 20 to 0.05 ppm. The following discussion gives a brief description of each of the risk assessments, summarizes the results

and offers OSHA's preliminary determination of the level of risk posed by exposure to EDB.

B. Terminology and Definitions

Several statistical/technical terms are defined here for reference in reading this section.

(1) *Mathematical model:* A well-defined mathematical equation describing the relationship between dose (e.g. parts per million of EDB) and response (e.g. number of tumor-bearing animals). The experimental data are used to define the relationship; that is, a curve is "fit" to the data.

(2) *Mathematical fit:* A term used to describe how close a predicted dose-response curve is to the actual observed points. Fit is often measured by a Chi-squared goodness-of-fit statistic and its corresponding P value. The closer the P value is to one, the better the fit.

(3) Several different mathematical models are discussed in this preamble. Most of the models are based on theories of cancer development, such as the onehit, the multistage, and the gamma multihit. The other models are usually applied to cancer studies but have also been used to predict risk for other actions of toxins.

a. Onehit model: This model assumes that the expected number of chemical-cell interactions is directly related to dose. The curve produced is linear in the low dose range. It can not take into account repair, detoxication reactions and metabolic activation.

b. Multistage model: This model assumes that the toxic response is the result of an ordered series of biological events and that the occurrence of each event is linearly related to the dose. [Note: The onehit model may be considered a special case of the multistage model, where there is simply one stage.]

c. Probit model: This is a typical sigmoid-shaped curve; strongest in the 5 to 95% response area. Zero responses are approached very rapidly as the dose decreases.

d. Logit model: This is also a sigmoid curve symmetric about the 50% response point. It approaches zero response more slowly than the probit model.

e. Weibull model: This is a generalization of the onehit model which allows for non-linear responses in the low dose region. The response may be concave or convex depending on estimates from the observed data sets.

f. Gamma Multihit model: This also assumes that an expected number of chemical-cell interactions is related to dose, but it further assumes that a number of responses is needed to produce the cellular response. Thus the model may fit data observed at higher doses better than the onehit model (Ex. 11, p. 100–102).

(4) *Extrapolation/interpolation:* Once a mathematical model is fit to a set of data points, one may wish to predict the risk at other points along the curve. Extrapolation is the prediction of risk outside the range of the observed data; interpolation is the prediction of risk within the range of the observed data. The term interspecies extrapolation refers to the prediction of risk in one species (e.g. man) based on observations in another species (e.g. rats).

C. Summary of Risk Assessments

OSHA prepared an in-house risk assessment (OSHA, 1981) based on the incidence of nasal cavity adenocarcinoma in the 1981 NCI inhalation bioassay in rats (Ex. 4–15). In the study, rats and mice were exposed to either 10 ppm or 40 ppm of EDB for 6 hours per day, 5 days per week for 78 to 103 weeks. In rats of both sexes, EDB induced cancer at both exposure levels, causing highly significant increases of nasal cavity adenocarcinomas as well as cancer at other sites. In mice of both sexes, EDB induced highly significant increases in lung cancer as well as cancer at other sites at the 40 ppm level. The incidence data used for this risk assessments given in Table 3. Though EDB has been shown to induce cancer in rats by several different routes of exposure (gavage, skin application, and inhalation) the NCI inhalation bioassay was chosen for the risk assessment since inhalation is the primary route of occupational exposure. This eliminates a potential source of uncertainty, the need to extrapolate from differing routes of exposure.

The OSHA in-house risk assessment also included a discussion of the impact of the choice of a scaling factor for dose. Doses are often scaled as a means of interspecies "standardization" in an attempt to account for interspecies variability in pharmacokinetic parameters (such as metabolism, absorption, distribution, as well as other factors that can affect the extrapolation process) (Hogan and Hoel, 1982).

In a table of dose equivalencies (OSHA, 1981, Table 4), conversion of animal doses to equivalent human exposure levels by adjusting for body surface area (mg/m^2) would increase the estimates of lifetime risk in humans by three to five fold (for a onehit model); adjusting for body weight (mg/kg) would decrease estimates of risk two to four fold at low exposures (for a onehit model). These effects would be more substantial with models of higher degree (quadratic, cubic, etc.). OSHA chose a scaling factor of one (i.e., ppm was an equivalent dose expression for rats and man) for two reasons: (1) Mathematically, the use of ppm as an expression of dose would produce median estimates of risk and (2) In a risk assessment based on nasal tumors, a contact tumor, dose expressed as air concentration (ppm) can reasonably be considered the effective dose (the dose actually causing an effect). OSHA's choice of ppm (i.e, a scaling factor of one) for nasal tumor risk extrapolation is supported by Busch of NIOSH (Memorandum to Director, 1982) and Brown (Ex. 11).

Data for each species were fit to two different mathematical models: the onehit model and the multistage model. These models were chosen because of their biological plausibility in describing chemical carcinogenesis. Both models assume no threshold, that is, that there is no demonstrated safe level of exposure. For the prediction of risk, it is further assumed that workers are exposed to a given level of EDB for 8 hours per day, 5 days per week, 46 weeks per year, for 45 years during a 54 year working lifespan.

Using the nasal tumor data, the in-house OSHA quantitative risk assessment predicted a range of 160 to 437 excess cancer deaths per 1000 workers at 20 ppm and 0.06 to 3 excess deaths per 1000 at 0.1 ppm (100 ppb).[3] These estimates were maximum likelihood estimates. 95% upper confidence limits on these estimates range from 251 to 516 excess deaths per 1000 at 20 ppm and 1.4 to 3.8 excess deaths per 1000 at 0.1 ppm (100 ppb) (Addendum, OSHA, 1981).

The EPA Carcinogen Assessment Group (CAG) reported an "Updated Quantitative Risk Assessment for Ethylene Dibromide" in 1979 which was updated in May 1980. The analysis predicts risk for dietary exposure from consumption of fumigated foods and crops grown in fumigated soil and occupational inhalation exposure.

For the latter risk assessment, the group employed preliminary data from the MRI/NIOSH inhalation study of ethylene dibromide and disulfiram (a note in the risk assessment states the pathological data was final; therefore the data would be the same as that found in Ex. 4–18). When Sprague-Dawley rats were exposed to EDB alone, statistically significant increases in spleen hemangiosarcomas and adrenal tumors were observed in male and female rats and a significant increase in

[3] A range of estimates over both species and both the onehit and multistage models.

mammary tumors was observed in the female rats. The tumor incidence data for the three types of tumors in the female rat and dose (expressed as mg/kg/day) were used to estimate the lifetime probability of cancer in humans. Tables of the incidence data employed in the risk assessment were not provided.

The CAG employed a one-hit model, adjusting for a 40 year work history and 71.3 year lifespan. This exposure scenario is slightly different from that usually employed by OSHA: 230 days per year for 45 years in a 54 year working lifespan in a 74 year lifespan. Using the CAG potency parameter (the unit risk per unit does, or slope of the curve) determined from the model, the excess probability of death from lifetime inhalation exposure to EDB at 20 ppm (7.95 mg/kg/day) is 999 deaths per 1000 workers, and 45 per 1000 workers at 0.1 ppm (100 ppb). In addition, the CAG risk assessment also included upper bounds risks due to ingestion of crops grown in soil fumigated with EDB, and foodstuffs fumigated with EDB. Though it is not the major source of occupational exposure, ingestion of fumigated foodstuff does pose some occupational risk.

The GAG commented on the suitability of the data for risk assessment. It endorsed these estimates of risk over previously derived estimates since "This [MRI/NIOSH] report allows us [CAG] to make a direct estimate of the carcinogenic effect of inhaled EDB" (p. 5).

Lastly, the CAG risk assessment also observed that the MRI/NIOSH report demonstrated that the carcinogenic effects of EDB were "considerably enhanced" when rats were exposed to disulfiram in addition to the EDB. The group estimated the potency of the combined exposure to be approximately 85 times that with EDB alone, indicating the potential for a highly synergistic effect with EDB. This concern for the potentiation of the toxic effects of drugs and chemcials like disulfiram is echoed in the NIOSH CIB (Ex. 4–6).

In an earlier (1978) risk assessment (Carcinogen Assessment Group 1978), CAG estimated risks due to occupational inhalation based on the negative epidemiology study reported by Ott et al. (1977). As was noted earlier, the results of the study must be examined carefully due to small sample size (and thus low statistical power) and mixed exposures. Using the methodology recommended by CAG in this risk assessment, OSHA estimated a 95% upper bound for the lifetime risk from exposure to EDB at 20 ppm to be 999 deaths per 1000 workers and 67 deaths per 1000 at 0.1 ppm (100 ppb).

Despite the limitations in the study results, the striking similarity of risk estimates produced from analysis of this human data extrapolation to the estimates based on the rodent inhalation study should be noted.

An even earlier CAG risk assessment (Memorandum to Edwin Johnson, September, 1977) was based on the NCI intubation study (Ex. 4–17). The risk assessment predicted a potency coefficient (slope) 16 times greater than that from the rat inhalation study. This risk assessment is reviewed in the 1979 CAG risk assessment.

SRI International (1982) performed a quantitative risk assessment [for NIOSH] based on the nasal tumors found in two inhalation studies in male rats, and males and female rats (NCI-NTP, 1981, Ex. 7–9, MRI/NIOSH, 1980, Ex. 7–4). By combining study results, there were data points for a control and three non-zero dose levels (10, 20 and 40 ppm) which were used for the risk assessment. Dose in ppm were scaled to mg/kg/day for the risk assessment and the data were fit to the gamma multihit and the multistage models. Predictions were made for workers both at rest and under working conditions.

SRI estimated the lifetime human cancer risk from exposure (working conditions) to EDB at 20 ppm to be 1.00 by the multistage model and .99 by the gamma multihit model (virtually 1000 cancer deaths per 1000 workers). Using the slopes and scaling factors provided in the risk assessment the risk at 0.10 ppm (100 ppb) as 117 excess deaths per 1000 (multistage model). Calculations based on other combinations of the data produced similar results.

TABLE 3.—SPECIFIC CANCER INCIDENCE IN RATS AND MICE

Species and sex	Exposure level (ppm)	Animals with tumors/animals examined
Rats		
Male	0	[1] 0/50
	10	*20/50
	40	*28/50
Female	0	0/50
	10	*20/50
	40	*29/50
Mice		
Male	0	[2] 0/41
	10	**3/48
	40	**19/46
Female	0	1/48
	10	***5/48
	40	**37/50

*P=0.001[3] **P=0.1523. ***P=1.1021.

[1] Nasal cavity adenocarcinoma/animals examined.
[2] Alveolar bronchiolar carcinoma/animals examined.
[3] P values are given for one-tail (upper tail) probabilities from Fisher's Exact Test.

In an interagency review of OSHA's in-house risk assessment, Busch of NIOSH outlined the major issues and uncertainties involved in all quantitative risk assessment (Memorandum to Director, 1982). In particular, he addressed the two main sources of error in such predictions: intraspecies extrapolation and interspecies extrapolations.

Busch criticized the OSHA risk assessment for not including confidence limits to account for variability in the test animals (intraspecies extrapolation). In response to this, OSHA has included and addendum to its in-house risk assessment which provides the 95% upper confidence limits on its estimates (OSHA, 1981).

Busch also included an analysis of the scaling of the dose parameter (interspecies extrapolation). He concluded (as had OSHA) that expressing dose in parts per million (ppm) or a scaling factor of one was the "best choice" for the nasal tumor data.

In addition, Busch discussed the use of the onehit and multistage models in providing "conservative" estimates of risk. (A conservative estimate is defined as an estimate which will tend not to underestimate the risk.) Busch pointed out that while the onehit and multistage models produced conservative (too high) estimates of risk at low doses, they actually *underestimate* the risk posed at levels which fall within the range of doses of the experimental animals, such as 20 ppm. Busch used a probit model to perform an alternative interpolation at 20 ppm EDB because he felt the convex-upwards shape of the probit model would probably be more accurate in the midrange than the linear or concave-upward multistage model. He added: "The onehit model is obviously not credible for use in the midrange" (p. 10). The risk estimates derived from the probit model exceed the OSHA in-house risk estimates at 20 ppm by 12% to 28%. Busch concluded:

> Based on a 45-year period of intermittent exposure (during 8-hour workshifts) to 20 ppm EDB, the risk (probability) that a worker will develop the most common form of cancer is estimated to be between 38% and 59%. This range is obtained from 95% two-sided confidence limits for risks to male and female rats. [There are indications] * * * that the risk estimates for rats exposed to 20 ppm EDB are probably underestimates of risks to humans at the same exposure concentration.

A detailed and informative risk assessment was performed by Brown under contract to OSHA (Ex. 11). He examined the mode of toxicity of EDB as a prelude to quantitatively estimating the cancer risk associated with occupational exposure.

Brown noted two types of tumors associated with EDB exposure—site of contact tumors and remote tumors. The target site of "direct" tumors was dependent on route of exposure. Oral doses of 20 and 40 mg/kg/day produced forestomach tumors (Ex. 4–17). Inhalation doses of 10 and 40 ppm 6 hours per day produced nasal cavity tumors (Ex. 4–15). Doses of 25 mg/mouse/day applied to the skin of mice produced skin papillomas and carcinomas (Ex. 4–19).

In addition, tumors were produced at tissue sites remote from the site of contact in each bioassay. These included respiratory tract (lung) tumors in mice in the skin painting study (Ex. 4–19); hemangiosarcomas of the circulatory system in rats in the inhalation studies (Ex. 4–15, 4–18), and alveolar/bronchiolar carcinomas in the inhalation studies in the mice (Ex. 4–15). In the oral gavage study, hemangiosarcomas were also produced in the circulatory system (Ex. 4–17).

The tissues remote from the site of direct contact in which tumors were produced would have had relatively low exposures to EDB (that is, the effective dose may be different than the administered dose). They presumably responded because of unique pharmacokinetic, metabolic or other biochemical factors. Since these remote site tumors may be of particular concern with chronic low level exposures (due to metabolite-EDB interaction), Brown recommended that risk to workers be based on the incidence of hemangiosarcomas in male rats; he suggested that a risk assessment based on nasal tumors may provide a "more conservative" alternative.

In making his quantitative estimates of risk, Brown relied on the following assumptions:

(1) Rats and mice can be used to predict the quantitative risk of human cancer, male reproductive injury and acute toxicity resulting in man from exposure to EDB. [Note: The quantitative risk assessment was based solely on cancer. Though there were dose-response relationships demonstrated for several reproductive effects in a variety of species, many of the endpoints (reduced egg production in hens, reduced average litter size in rats) maybe inappropriate for quantitative risk assessment for humans].

(2) Cancer and other health risks at low doses are proportionally lower than risks at high doses. The low-dose extrapolation can be accomplished by fitting a mathematical dose-response model to the experimental data.

(3) Since the primary route of exposures in workers is inhalation, data from inhalation studies may be more applicable to hazard assessment for workers than data from oral or dermal routes of exposure, although significant actions are produced by skin contact.

(4) Both EDB and its major metabolites contribute to the human carcinogenic risk. The relationship between dose level of the exposure, the dose absorbed, and the risk of specific tumors differs for direct contact tumors and tumors remote from the site of contact.

(5) The exposure level and dose on a mg/kg body weight basis will possibly affect the relative amount of each metabolite(s) formed and the site of action of EDB.

(6) The human epidemiology studies available are insufficient for quantitative risk assumptions but are useful for verifying predictions developed from models based on the animal data.

Justification for these assumptions is detailed in Brown's report. Assumptions 1–3 and 6 were also made by OSHA in its in-house risk assessment; since the OSHA in-house risk assessment was based on nasal (site of contact) tumors however, assumptions (4) and (5) were not applicable.

In an effort to make maximal utilization of the available information, Brown chose to combine the results of two inhalation studies in rats in order to estimate the risk to workers, as was done in the SRI risk assessment. Data on specific tumors (i.e., nasal tumors or hemangiosarcomas) from different sutdies were combined when it was felt that they resulted from similar biological mechanisms. The integrity of this procedure was borne out by the comparison of predictions using combined data with those from risk assessments based on other data sets, particularly estimates based on single data sets from single experiments. Brown's preferred estimates were based on the combined data from the NCI/NTP and MRI/NIOSH inhalation bioassays.

Brown scaled the dose for risk assessment based on the remote tumors (hemangiosarcomas) in mg/kg/body weight. However the risk estimates based on nasal tumors used dose in terms of ppm (a scaling factor of one) since he believed that when "tumors are to a high degree the result of a direct action (Alkylation) by EDB, then the absolute concentration reaching the issue would be a more important parameter than the dose to the animal on a body weight basis." (p. 108).

Where possible, Brown fit six different models (onehit, multistage, probit, logit, gamma multihit and Weibul) to the data. His preferred estimates were those from the onehit model using nasal tumor data and the onehit and multistage models when using hemangiosarcoma data.

Based on the hemangiosarcoma data (Ex. 4–15, 4–18), Brown predicted a risk of 70 to 10 excess cancer deaths per 1000 workers at 20 ppm with 95% upper confidence limits of 134 to 148 excess deaths per 1000; at the proposed OSHA PEL of 0.1 ppm (100 ppb), he predicted an excess risk of 0.2 to 0.6 excess deaths per 1000 (95% confidence limits are .7 and .8 excess deaths per 1000). Again, using the inhalation studies, estimates of risk based on nasal tumor incidence (and air concentration of EDB—ppm) were 725 excess deaths per 1000 workers at 20 ppm and 6 excess deaths per 1000 at 0.1 ppm, with 95% upper confidence limits of 785 (at 20 ppm) and 8 (at 0.1 ppm) excess deaths per 1000.

Another risk assessment demonstrating the risk associated with EDB was given in the "Proposed Emergency Standard for Ethylene Dibromide" for the State of California (Ex. 4–9, Appendix G). This quantitative assessment of risk utilized data from the NCI inhalation bioassay. Though data from the NCI gavage bioassay are discussed in the submission, the estimates of lifetime cancer risk were based on data from the inhalation bioassay "since this route of exposure is similar to what may be the major source of human exposure" (pg. 93). The data used in the CAL/OSHA risk estimates is the nasal tumor data employed in the OSHA in-house risk assessment (OSHA, 1981) given in Table 3. This risk assessment used a mg/kg/day dose-equivalency with a daily lifetime occupational exposure of 1 ppm equivalent to 0.32 mg/kg/day. Using a simple linear model, the CAL/OSHA risk assessment predicts a lifetime risk of cancer from occupational exposure to EDB as 400 per 1000 at 20 ppm and 2 per 1000 at 0.1 ppm (100 ppb); using the onehit model the risk is greater than 996 per 1000 from exposure at 20 ppm and 0.5 per 1000 at 0.1 ppm (100 ppb).

D. Discussion and Conclusions

A summary of results from each of these quantitative risk assessments is given in Table 4. Taken together, they establish that there is a large excess risk of cancer death from exposure to EDB at 20 ppm and that lowering the PEL to 0.1 ppm will greatly reduce that risk.

Estimates of the excess risk at 20 ppm ranges from 70 to 999 per 1000 and depend heavily on the model used and the choise of tumor data upon which the quantitative risk assessment is based. After examining these (eight) risk

assessments, OSHA endorses Brown's approach to the quantitative assessment of risk from exposure to EDB. OSHA concludes that

TABLE 4.—ESTIMATES OF LIFETIME EXCESS CANCER RISK FROM EXPOSURE TO ETHYLENE DIBROMIDE

Risk assessment	Excess deaths per 1,000 (95 pct upper confidence limits)		Model
	20 PPM	0.1 PPM	
EPA CAG:			
1978	999	67	"Upper bound" on one-hit.
1980	999	48	One-hit.
SRI	990–1000	117	Multi-hit, one-hit.
OSHA in-House	190–437(251–516)	0.08–3(1.4–3.6)	One-hit, multistage.
Busch	190–490(293–586)		Probit.
Brown:			
Hemangiosarcomas	70–110(134–146)	0.2–0.8(0.7–0.8)	One-hit, multistage.
Nasal Tumors	725(795)	8 (8)	One-hit.
CAL/OSHA	400–999	0.5–2	One-hit, linear.

Brown's risk estimates which incorporate the combined hemangiosarcoma data and the combined nasal tumor data are to be relied upon in making its preliminary determination of risk. Thus, at this time, OSHA concludes that the lifetime estimate of risk from (lifetime) occupational exposure to EDB at 20 ppm is 70 to 110 excess deaths per 1000 (95% upper confidence limits of 134 to 148 excess deaths per 1000); the predicted risk at 0.1 ppm (100 ppb) is therefore 2 to 6 per 10,000 with 95% upper confidence limits of 7 and 8 per 10,000. The estimate of 725 excess deaths per 1000 based on the nasal tumors is considered a valid but conservative estimate of risk. The rationale for these conclusions is given below.

OSHA believes that the multistage model (and the one-hit model as a special case) is the most appropriate model for the prediction of excess risk from exposure to EDB. The curve shows good fit to the observed data and was employed in almost all the quantitative risk assessments submitted to the record.

Busch's (NIOSH) contention that the nonsigmoid curves tend to underestimate the risk in midrange is not borne out by Brown's data. Estimates from the sigmoid curves at 20 and 10 ppm are almost identical to those calculated for the one-hit and multistage models (71 per 1000 for the probit model). This could be a result of the different tumor data used by Brown (hemangiosarcomas) or the increase in degrees of freedom gained in the combination of data sets. The "conservatism" of one-hit and multistage models at low doses is still evident with this data (probit estimate is 5.0×10^{-9} per 1000 at 0.1 ppm).

The choice of the hemangiosarcoma data for the risk assessment was particularly prudent. Hemangiosarcomas were observed in all of the bioassays. The bioassays indicate that, regardless of route of exposure (inhalation, oral gavage, skin painting), the spleen and the circulatory system are specific target organs for the action of EDB and its metabolites. EDB is absorbed across biological membranes and found in circulating blood as EDB. This, EDB is available to all perfused tissues (essentially all tissues).

As Brown pointed out, "The tissues remote from the site of direct contact in which tumors were produced would have had relatively low exposures to EDB. They presumably responded because of unique pharmacokinetic, metabolic or other biochemical factors . . . These remote site tumors may be of particular concern with cronic low level exposures [due to metabolite-EDB interaction]" (Ex. 11, p. 94).

In addition, OSHA recognizes the advantage of combining data sets of similar tumors for risk assessment as was done by SRI (1982) and Brown (Ex. 11). Not only do similar results from different studies strengthen the weight of evidence of carcinogenicity, but the combination of these data into a single prediction of risk is resonable and provides a wider data base (more degrees of freedom) from which to make the prediction of risk.

The choice of a dose scaling factor for calculating equivalent doses was mixed among the submissions. The CAG, SRI, and CAL/OSHA assessments employed a factor to convert to mg/kg/day for risk assessment based on the inhalation bioassays and nasal tumor data. OSHA, Busch (NIOSH) and Brown employed ppm (scaling factors of 1) for these analyses, Brown recommending use of mg/kg/day only for the systemic (non-contact) tumors. OSHA concurs with this approach. The use of a mg/body weight scaling factor adjusts in some way for differences in biological mechanisms between species and seems to be a more accurate characterization of dose for remote site tumors. As Brown notes, use of actual concentration seems reasonable in a risk assessment based on contact tumors.

The excess cancer risk to workers exposed to EDB with high intermittency has not been quantified in this risk assessment. The models employed by OSHA and others assumed a cumulative dose-risk relationship. Moreover, risk estimates were based on results of cronic exposure bioassays.

In most industrial settings and other work environments, employee exposures to harmful substances are regular and long term in nature. Based upon the limited data presently available, OHSA believes that the exposure pattern for many EDB-exposed employees may follow a different pattern and that a substantial number of employees may be exposed to EDB on a somewhat irregular or intermittent basis. The models relied upon by OSHA and others to estimate the risk from occupational exposure to EDB assume regular long-term exposure. Similarly, the risk estimates were based on the results of *chronic* exposure bioassays. Therefore, the risk estimates discussed herein may only be imprecisely related to the portion of the population which is exposed to EDB on a less than regular basis and may not offer a fully representative description of these workers' risk.

A wide variety of factors makes it difficult to account for these highly intermittent exposure patterns in a quantitative manner. There is no widely accepted risk model presently in use which provides the opportunity to consider the effects of intermittent exposures or periods of non-dosing. While it is possible to adjust the mathematical models to reflect a decrease in total exposure time (which by definition is always present with highly intermittent exposures), the mathematical models cannot evaluate or predict the range of boiological interference which may take place between exposures. On the one hand, there may be elimination or deactivation of EDB to some extent when it is introduced into the system in small quantities at infrequent intervals. Such a highly intermittent exposure pattern may, at least theoretically, allow for the repair of damaged systems or cells. Both of the factors then may result in a greater reduction of risk than a model simply adjusted for decreased exposure time might reflect. On the other hand, very little deactivation or repair may

occur in spite of relately sporadic exposures.

The impact of intermittent or sporadic exposures to EDB is particularly difficult to weigh because of the lack of precise knowledge of the biological mechanism of carcinogenesis EDB has been shown to cause cancer in test animals by every route of exposure; tumors have been produced at the site of contact as well as remote sites. Experimental evidence shows that EDB forms various metabolites once it is introduced into the system; some of these metabolites are active mutagens. Moreover, EDB and its metabolites are potent alkylating agents; alkylation of macromolecules has been identified as the primary step in toxic injury to the cell in the case of reactive molecules. Consequently it may be inappropriate to assume that repair or detoixification play a significant role in spite of intermittent exposure.

Moreover, the only scientific evidence specific to EDB which is presently available suggests that the risk of cancer is not significantly reduced in spite of an intermittent dosing pattern. In the NCI oral gavage study test animals were subjected to 13 weeks at high doses followed by approximately 71 weeks at a lower dose on a cyclic basis (the animals were exposed for 4 weeks and rested for 1 week). Although the animal exposures in this study could be described as intermittent, the test animals developed cancers in the same order of magnitude as in other studies where the animals were subjected to regular exposures. Consequently, any repair or deactivation that does occur may be extremely dependent on the spacing of the doses and there is no reason to believe that in the case of EDB exposure there is a linear relationship between the repair mechanism and dose.

Another factor to be considered is that EDB is a proven synergistic agent. In view of the fact that EDB may act in a synergistic manner with other substances to which the worker is exposed, the potential effect that intermittent exposures to EDB may have on the biological system must be taken into account. This factor is especially important since workers are often exposed to other carcinogens in the work environment as well. (For example, grain elevator workers who may be intermittently exposed to EDB are sometimes also exposed to carbon tetrachloride, a well-documented carcinogen). Consequently there may be no reduction of the risks or there may be an actual increase in risk even though the EDB exposures are intermittent.

Based upon its present knowledge, OSHA feels that its ability to quantify the risks of intermittent exposure to EDB is limited. That is, limitations in the available data and science are such that a quantifiable extrapolation of risk for intermittent exposure to EDB is not possible at this time. OSHA requests information and data specifically addressing the question of intermittency; in particular, information is needed on the appropriate modeling and the prediction of risks due to intermittent exposure at high and low exposure levels.

OSHA predicts that the increase in lifetime cancer risks attributable to exposure to EDB at the current PEL is 7 to 11%, with possible upper limits as high as 79%. OSHA believes that such risks warrant and compel a new standard (and lower PEL) for occupational exposure to EDB. The impact of these estimates of risk and their role in setting the new PEL is discussed in the following section.

V. Significance of Risk

OSHA's overall analytic approach for setting worker health standards is a four step process consistent with recent court interpretations of the OSH Act and rational, objective policy formulation. In the first step, quantitative risk assessments are performed where possible and considered with other relevant factors to determine whether the substance to be regulated poses a significant risk to workers. In the second step, OSHA considers which, if any, of the proposed standards being considered for the substance will substantially reduce the risk. In the third step, OSHA looks at the best available data to set the most protective exposure limit that is both technologically and economically feasible. In the fourth and final step, OSHA considers the most cost-effective way to achieve the objective.

In the Benzene decision, the Supreme Court indicated when a reasonable person might consider the risk significant and take steps to decrease it. The Court stated:

> It is the Agency's responsibility to determine in the first instance what it considers to be a "significant" risk. Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2% benzene will be fatal a reasonable person might well consider the risk significant and take the appropriate steps to decrease or eliminate it. (*I.U.D.* v. *A.P.I.*, 448 U.S. at 655).

The Court indicated, however, that the significant risk determination required by the OSH Act is "not a mathematical straightjacket," and that "OSH is not required to support its findings with anything approaching scientific certainty." The Court ruled that "a reviewing court [is] to give OSHA some leeway where its findings must be made on the frontiers of scientific knowledge [and that]" * * * the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of overprotection rather than underprotection." 448 U.S. at 655, 656.

As indicated in the health effects section above, EDB is an extremely potent carcinogen in animals, causing cancer by all routes of exposure, both at the site of contact and at remote sites.

In the preamble to this proposed standard, OSHA has presented data establishing a dose response relationship with regard to cancer in experimental animals as well as hepatic necrosis, toxic nephropathy and reproductive toxicity including embryo toxicity. Mutagenic effects have also been established. In order to determine whether the risk from exposure to EDB is "significant" the agency examined the risk from cancer from such exposure. No quantification of risks based on the numerous other adverse health effects associated with EDB exposure was attemped. Virtually all of the risk assessments performed (see discussion below) demonstrate that the risk of cancer from EDB is so high at such low levels of exposure that any further quantitative inquiry is rendered superfluous. However, OSHA believes that experimental data yields sufficient qualitative evidence to support the conclusion that EDB is a direct acting mutagen which also metabolizes to one or more highly mutagenic compounds. In addition, laboratory evidence suggests that EDB or an alkylating metabolite of EDB is responsible for the adverse reproductive effects observed.

As discussed in detail earlier, OSHA has based its risk estimates on a quantitative risk assessment for EDB performed by David Brown of Northeastern University (Ex. 11). Brown based his risk assessment on the inhalation studies conducted by the National cancer Institute/National Toxicology Program (NCI/NTP) and NIOSH/Midwest Research Institute (NIOSH/MRI). Brown's risk assessment predicted a risk of 70 to 110 excess cancer deaths per 1000 workers exposed at the current permissible exposure level (20 ppm) based on the hemangiosarcoma data combined from both studies. Estimates of risk based on nasal tumor incidence were 725 excess deaths per 1000 workers exposed at 20 ppm. These risk estimates assume employees have

regular exposure to the EDB over their working lifetime (45 years).

These estimates of risk for exposure to EDB at the current exposure limit greatly exceed the one per thousand guideline which the Supreme Court has characterized in the benzene case as presenting a significant risk. If workers are exposed for less than a working lifetime, as may be the case for citurs workers, the risk might be somewhat reduced. However, at this point, OSHA does not know how to quantify any possible reduction of risk (see discussion below). Public input is requested on this issue. It should be noted, however, that the laboratory evidence indicates that the risk to workers exposed at the present permissible exposure level of 20 ppm is so great that even if a scientifically valid methodology could be developed to account for intermittency, which might result in reducing the lifetime risk estimates for certain segments of the population, perhaps even by a factor of 2 or 3, risk would nevertheless still greatly exceed the one per thousand which the Supreme Court gave as an example of a significant risk *(I.U.D.* v. *A.P.I.,* 448 U.S. at 655).

Moreover, at least in the case of nasal tumor, the risks from EDB exposure appear to be far greater (725 per 1000) than for any other hazard that OSHA has regulated in the past, where the risks have been quantified. In the arsenic regulation, for example, the risk of cancer at the former permissible exposure level was estimated to be 400 per 1000. (see supplemental statement of reasons, 48 FR 1901), which was found to be significant. In addition, OSHA's preliminary risk assessment (which concurs with Brown's) indicates that the risk of cancer from EDB exposure at the permissible exposure level (using the combined hemangiosarcoma data) is at least as high (70 to 110 per 1000) as risks from other hazards to which OSHA has responded in those cases where quantification has been attempted. For example, the risk of cancer (using the combined hemangiosarcoma data) from EDB exposure is comaparable to the risk of cancer from ethylene oxide exposure, estimated at 63 to 109 per 1000, which OSHA preliminarily found to be significant in its recently proposed ehtylene oxide standard (48 FR 17295) and to the risk of byssinosis from cotton dust exposure of approximately 83 per 1000. Further, the risk from exposure to the current permissible exposure limit for EDB is much greater than the risk to coke oven workers (approximately 10 per 1000) which the Agency determined was sufficient to justify lowering the permissible exposure limit.

OSHA also evaluated the extent to which the risk would be reduced by adopting the proposed permissible exposure limit of 0.1 ppm. Assuming exposure over a working lifetime, the risk estimates made from the combined hemangiosarcoma data indicate risk would be reduced from 70 to 110 excess deaths per 1000 at the crrent premissible exposure limit to 2 to 6 excess deaths per 10.000 at the exposure limit contemplated in the proposed standards, approximately a 94.5% reduction in risk. If the risk estimates predicted from the nasal tumor data are used, the risk would be reduced from 725 excess deaths per 1000 at the current permissible exposure limit to 6 per thousand at the proposed permissible exposure level, indicating a 99% reduction in risk. Therefore, it appears that the excess deaths from cancer will be substantially reduced if the proposed permissible exposure level is adopted.

OSHA used the onehit and mulistage models to determine risk at both the current and proposed EDB permissible exposure limits and concluded that the multistage model was the most appropriate in this instance. It should be noted that estimates calculated using the onehit model were either the same or higher than those generated by the multistage model primarily relied upon by OSHA. Brown also calculated risk using other models, including the probit, logit, Weibull and gamma models where there were enough data points for these models to be used. Using the combinded inhalation study data, these various models estimated excess risks at the current permissible exposure limit which were essentially consistent with those generated by the multistage model; excess risk estimates generated by the other models (probit, logit, Weibull and gamma) at the proposed permissible exposure limit were somewhat lower that those calculated by the multistage model (Ex. 11, pp. 111–120). In any event, *all* models indicate an extremely high excess risk at the current permissible exposure limit and a dramatically reduced risk at the proposed permissible exposure limit. This corroborates OSHA's finding that there is a significant risk from exposure to EDB at the permissible exposure limit which will be significantly reduced by adopting the proposed permissible exposure limit and other proposed provisions designed to reduce worker exposure to EDB.

OSHA's risk assessment projects that a maximum likehood estimate of risk of 2 to 6 cancer cases per 10,000 workers will occur from regular occupational exposure at 0.1 ppm over a working lifetime. The upper confidence limit of this assessment is 7 to 8 cases per 10,000 workers. A more conservative estimate based upon the nasal tumor data indicates that at the proposed permissible exposure limit there will be 6 cancer cases per 1000 workers (with an upper confidence limit of 8 per 1000).

OSHA's preliminary conclusion is that risk is not eliminated at 0.1 ppm PEL. While the risk at this level ranges from approximately .2 to 6 cancers per thousand workers depending upon which laboratory results (tumor types) are relied upon, it is not necessary to determine which is the best estimate. Neither estimate reduces the risk to the point of insignificance. The proposed permissible exposure limit is based upon feasibility considerations. In other words, after evaluating all of the information which is presently available to it, the agency believes that it is feasible for employers to reduce employee exposures to EDB to 0.1 ppm and it may not be feasible to reduce exposure below 0.1 ppm.

Congress passed the Occupational Safety and Health Act of 1970 because of a determination that occupational safety and health risks were too high. Based on this, it is clear that Congress gave OSHA authority to reduce risks of average or above average magnitude when feasible. OSHA believes that the proposed standard for EDB will reduce the very significant risk from exposure to EDB to between .2 to 6 per 1000. Therefore, the Agency is carring out the congressional mandate within the limits of feasibility and is not attempting to reduce insignificant risks.

Under both the Congressional intent and the Supreme Court rationale, OSHA must, if it is feasible, seek to reduce risks below those estimated by the risk assessment to persist at a PEL of 0.1 ppm. The proposed rule as drafted may be expected to reduce the risks of EDB exposure below those estimated using the mathematical models because the estimates of risk only consider the PEL and do not take into account other protective clothing and work practices. As OSHA's assessment of the risk incorporated only the estimates from the inhalation of EDB, OSHA believes that these other protective provisions may lead to further reductions in risk by controlling exposures by other routes, namely dermal exposure and ingestion. OSHA believes that exposures by these other routes may contribute substantial additional risk to workers. However, the decrease in risk that may be achieved by these additional worker protection

provisions has not been quantified beyond a determination that they will add to the protection provided by a lower PEL. OSHA believes that employers who fulfill the provisions of the standard as proposed will provide protecion for their employees from the hazards presented by occupational exposure to EDB well beyond those which would be indicated solely by the reduction of the PEL.

In determining the level to which the permissible exposure limit should be lowered, several alternative 8-hour TWA's (1, 0.5, 0.1 ppm) were considered by the Agency. OSHA currently believes that compliance with a 0.1 ppm TWA is technologically and economically feasible based on data discussed elsewhere in this document and the Regulatory Analysis.

As discussed above, there may be a large segment of the exposed population that is exposed to EDB only intermittently. This pattern of exposure appears to be most likely for citrus workers as well as those in flour mills and grain elevators. In such cases, the risk of exposure to EDB may be somewhat lower than that predicted by the various risk assessment which assume regular exposure over a working lifetime. At this point, however, OSHA is unable to quantify with any degree of confidence any possible reduction of risk as a result of intermittent exposures.

The Agency believes that it may be possible to describe the risk posed by intermittent exposures in a more quantitative manner. Therefore, the risk estimating methodology employed as well as the rationale for the reliance upon specific data and assumptions is described in some detail (see Quantitative Risk Assessment discussion of the preamble) and advice is solicited from the scientific community on how to refine the technique to account for highly sporadic as well as seasonal exposure patterns.

As noted above in the quantitative risk assessment discussion, the Agency is mindful of the fact that there may be considerably more involved in accounting for intermittency than merly adjusting the total dose considered in the various risk assessment models. Therefore, OSHA invites comments addressing the issue of whether there are scientifically valid and and well-accepted techniques for accounting for intermittency in the extrapolation from laboratory data to man when the laboratory studies themselves are based upon chronic and not intermittent exposure.

In spite of these considerations, the Agency believes that the risk assessment relied upon in this proposal represents the best quantification of risk available at this time. Moreover a number of nonquantitative factors lead OSHA to believe that in spite of the intermittent exposure patterns of certain segments of the exposed population, the risk from these exposures may be close to that described in the risk assessment.

It should be noted that the NCI oral gavage study, the only laboratory study which may be analogous to intermittent exposures, showed cancers in the same order of magnitude as other studies that approximated regular exposures. In addition, dermal exposure may make a significant but unquantifiable contribution to the total EDB exposure of some industry segments such as citrus handling, where the exposure to airborne EDB may be characterized as seasonal. Although these dermal exposures are not taken into account in any of the risk assessments, the possibility of dermal exposure even when there are no spashes or spills of EDB cannot be discounted. For example, tests of fumigated citrus in Texas revealed a residual layer of EDB on the surface of the fruit of approximately 4.5 ug 14 hours after fumigation; this level was substantially reduced to 0.8 ug 40 hours after fumigation (OSHA Technical Submission #3).

The extreme toxicity of EDB is underscored by the laboratory results. EDB and two of its principal metabolites have been shown to be positive mutagens. Various types of tumors were produced at tissue sites remote from the site of contact in each bioassay. These included respiratory tract tumors, hemangiosarcomas of the circulatory system and alveolar/bronchiolar carcinomas. In addition, contact site tumors were induced in the forestomach and nasal areas. Adverse reproductive effects of EDB in several animal species have been clearly established. These adverse effects include interference in the early stages of sperm development and reduction of sperm count; malformation and anomalies in offspring were also produced. Moreover, there is an indication that some reproductive effects may be based on short term peaks, totally unrelated to length of exposure (Ex. 11).

OSHA believes that the total risk to employees exposed to EDB is the result of the compounded risks from carcinogenicity, mutagenicity, spermatotoxicity and damage to the kidneys, liver, spleen, respiratory tract, central nervous system, skin and eyes described in laboratory studies. All of these things together lend qualitive support to OSHA's quantitative risk assessment for those exposed continuously on a daily basis as well as for those exposed on an intermittent or seasonal basis.

The Agency believes that while the proposed PEL may be conservative for some industry segments who are not exposed to EDB on a regular basis, OSHA concludes that based upon current knowledge there is support for the proposal which applies the proposed PEL of 0.1 ppm to all covered employees regardless of their exposure pattern. This is especially true in view of the fact that the Agency has limited knowledge as to the precise exposure profile within various segments of the industry. In other works, while the average range of exposures are known for various groups, it is difficult to say with any degree of certainty exactly what the exposure duration and pattern is (that is, number of day, weeks and months, and frequency) for all members of these exposed groups. Ferthermore, the Supreme Court in the Benzene decision indicated that the Agency was free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of overprotection, rather than underprotection (448 U.S. 656) and did not have to support its findings with anything approaching scientific certainty. This is of course consistent with the statutory mandate to protect *every* working man and woman insofar as possible from material impairment.

The Agency will continue to seek a more scientifically precise method for accounting for intermittency of exposure. If such a method can be found and if scientific evidence supports the proposition that the risk from intermittent exposure decreases significantly, then OSHA may consider some adjustment in the proposed PEL for various industry segments.

VI. Summary of Regulatory Impact and Regulation Flexibility Analysis

A. Introduction

Executive Order 12291 (46 FR 13197, February 19, 1981) requires that a regulatory analysis be conducted for any rule having major economic consequences on the national economy, individual industries, geographical regions, or levels of government. The Regulatory Flexibility Act (5 U.S.C. 601 et. seq.) similarly requires the Occupational Safety and Health Administration (OSHA) to consider the impact of the proposed regulation on small entities.

In accordance with these requirements, OSHA has prepared a Preliminary Regulatory Impact and

Regulatory Flexibility Assessment for the ethylene dibromide (EDB) standard. This assessment describes the industries affected by the standard, the regulatory alternatives, the effects of non-regulation, the costs of compliance with the proposed standards, the technological feasibility of the proposed provisions, and some of the potential benefits that will occur to employees exposed to EDB at their places of work.

The Secretary has determined that this action would not be major as defined by Section 1(b) of Executive Order 12291. The Secretary also certifies that this action would not have a significant impact on a substantial number of small entities as defined by the Regulatory Flexibility Act. The Preliminary Regulatory Impact and Regulatory Flexibility document is available in the docket office for inspection and copying.

B. Summary of Industry and Exposure Profiles

OSHA estimates that the proposed EDB standard would cover approximately 600 continuously exposed employees and about 56,400 intermittently exposed workers in seven industry sectors. Continuously exposed employees are defined as those exposed on a daily basis such as in the manufacturing of EDB. In termittently exposed employees are defined as those exposed on a seasonal or periodic basis such as those in the citrus industry.

The employees covered by the proposed standard work in seven industry sectors: EDB manufacturing; pesticide formulating; manufacturing of gasoline antiknock compounds and their blending; handling of fumigated citrus, grain, and papaya; and flour mill equipment fumigation. The EDB manufacturing industry is comprised of 4 large firms (one firm recently ceased manufacturing EDB), only 1 of which has annual sales under $1 billion. OSHA has identified 18 firms with 20 plants that blend and repackage EDB for pesticides. No firm had annual sales less than $0.5 million. Four firms manufacture antiknock compounds that contain EDB. These firms all had annual sales of more than $500 million. Six Hawaiian packinghouses handle fumigated papaya. Five out of six of these firms are relatively small, averaging 24 processing employees each. The average value of fresh utilized production for the 1980–1982 growing season was about $11 million.

OSHA has determined that approximately 2,800 employees are exposed seasonally in the handling of fumigated citrus. Outside of California, workers that are exposed to EDB in this industry include Florida and Texas truckers, Texas packinghouse employees, and Florida and Texas longhoremen and warehousemen. Those jurisdictions covered by the State of California's EDB standard (CAL/OSHA) are excluded from this analysis because they are presumably in compliance with the State plan standard and therefore they would incur no additional compliance cost.

Florida orange production was valued at over $1 billion in the 1980–81 crop season and Texas grapefruit production was valued at almost $250 million in the same time period. One industry uses EDB in the fumigation of flour mill equipment. Approximately 275 firms with about 8,000 employees are exposed to EDB periodically in this industry. Firms with less than 20 employees had annual sales averaging nearly $500,000 (in 1972 dollars) and firms with 20 or more employees had annual sales averaging over $10 million. Grain elevators use EDB to fumigate grain in storage. About 7,550 country elevators employing about 45,000 employees are exposed to EDB on the average less frequently than employees in these other industries.

C. Summary of Benefits

In its evaluation of the cancer potential of EDB exposure, OSHA finds that for every 1,000 workers continuously exposed over a working lifetime, EDB would cause between 70 and 725 cancers at exposures of 20 ppm, between 1.7 and 62 cases at 1 ppm, and from 0.2 to 6 cancers at 0.1 ppm. On the basis of current exposure estimates for the roughly 600 workers who are continuously exposed to EDB on a daily basis, these risks indicate that EDB would cause between 1 and 8 cancers in this group. Compliance with the proposed standard would reduce this number to 0 to 3 cancers.

OSHA has not yet estimated the number of cancers that EDB would cause among the approximately 56,000 workers exposed on a less than daily basis and is soliciting information from the scientific community on the appropriate means to quantify the risks to these workers. A number of factors, however, lead OSHA to believe that the risks resulting from these intermittent exposures are significant. For example, the NCI oral gavage study, which is the only laboratory study that may be analogous to intermittent exposures, showed cancers in the same order of magnitude as studies based on continuous exposures. In addition, dermal and oral exposure may make a significant but unquantifiable contribution to the total EDB exposure of some industry segments, such as citrus handling, where the exposure to airborne EDB may be characterized as seasonal. Although these dermal exposures are not taken into account in any of the risk assessments, there is a real possibility that dermal exposure contributes to total exposure even when there are no splashes or spills of EDB.

Moreover, OSHA believes that the hazard to employees exposed to EDB is not limited to cancer but reflects the compounded risks from carcinogenicity, mutagenicity, spermatotoxicity and damage to the kidneys, liver, spleen, respiratory tract, central nervous system, skin, and eyes. While data are not available to permit the frequency of these effects to be precisely predicted, together they support OSHA's determination to promulgate a regulation that protects all employees exposed to EDB.

D. Technological Feasibility

OSHA has examined the technological feasibility of the proposal and concluded that, based on available data, the proposal is technologically feasible across all of the affected industries examined. However, OSHA has not yet obtained complete data to determine the technological feasibility of engineering controls for those firms that are engaged in the manufacture of antiknock compounds and their blending. OSHA has hired Centaur Associates to complete this assessment and their findings will be available during the public participation period.

E. Summary of Costs

Based on the data currently available, OSHA estimates that the annual cost of complying with the proposed standard would not exceed $3.9 million. Consequently, this regulation is not a "major rule" as defined by the criteria of Executive Order 12291. These annual costs include $51,500 for EDB manufacturers, $96,100 for EDB pesticide formulators, and $675,200 for those firms that handle fumigated cirtrus. The annual costs also include $3.05 million for flour mills and $39,400 for firms that handle fumigated papaya. Grain elevators are likely to incur few costs because they should be able to discontinue the use of fumigants that contain EDB and to substitute other fumigants. To supplement these findings, OSHA has contracted with Centaur Associates to gather additional data to characterize the proposal's impact on the compliance costs, technology, and economic status of these industry sectors. In addition, Centaur is gathering similar data for firms engaged in the

manufacturing and blending of antiknock compounds. These findings will be made available during the public comment period.

Medical surveillance and respiratory protection account for more than two-thirds of the annual compliance costs estimated to be incurred by firms in these affected industries. Medical surveillance is expected to cost approximately $1.6 million, or 41 percent of the annual compliance costs, and respiratory protection is estimated to cost about $939,000 or 24 percent of the annual compliance costs. The costs to install engineering controls accounts for less than 13 percent of the annual costs.

F. Economic Impacts and Regulatory Flexibility Analysis

This regulatory assessment also considers whether the industries affected by the standard would remain economically viable after compliance with the provisions of the proposal. The assessment concludes that compliance with the proposed EDB standard would have no significant economic impacts on EDB manufacturers and users. Available data indicate that compliance costs would be no more than 0.1 percent of total sales in any of the affected industries. In view of the relatively small magnitude of these costs, any effect on prices and output would be almost negligible. While data on the profitability of individual firms are not yet available for all the affected industries, information regarding the magnitude and distribution of compliance costs among the affected firms indicates that the proposal should not adversely affect these firms' competitive abilities.

Pursuant to the Regulatory Flexibility Act of 1980 (Pub. L. 96-353, 94 Stat. 1164 [5 U.S.C. 601 et seq.]) OSHA has given special consideration to the mitigation of the economic impacts of the proposed standard on small entities. OSHA does not anticipate that the proposed standard would adversely affect small entities. Nevertheless, OSHA seeks additional data on this subject as few responses to OSHA's Advance Notice of Proposed Rulemaking concerned economic impacts. Further attempts to design a standard to minimize the relative impact on small entities, while ensuring safety and health in the workplace, will depend upon the information obtained during the forthcoming public participation period.

VII. Environmental Impact

On December 18, 1981, OSHA published an Advance Notice of Proposed Rulemaking (ANPR) (46 FR 61671-76) for occupational exposure to ethylene dibromide (EDB). Information was solicited from the public on a variety of issues including environmental impacts of a proposed revised standard. The comment period for this ANPR ended on May 31, 1982. The information and comments submitted in response to the ANPR have been reviewed in acccordance with the requirements of the National Environmental Policy Act (NEPA) of 1969 (42 U.S.C. 4321, et seq.) the Guidelines of the Council on Environmental Quality (40 CFR Part 1500), and OSHA's DOL NEPA Procedures (29 CFR Part 11). As a result of this review, the Assistant Secretary has determined that the proposed rule will not have a significant impact on the environment external to the workplace. Impacts onthe workplace environment are discussed in other portions of this preamble.

EDB is used in the manufacture of antiknock additives for gasoline, as a spot fumigant on cereal and grain handling equipment, as a soil fumigant, as a source of bromine in organic synthesis processes, in the manufacture of vinyl bromide, as a catalytic agent, and as a specialty solvent for resins, gums, and waxes.

The Environmental Protection Agency (EPA) has the authority to regulate the use and application of EDB as a fumigant under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as amended (7 U.S.C. 136 et seq.). EPA regulations on the enforcement of FIFRA are found in 40 CFR Part 162. As a fumigant, the formulations of EDB pesticides are registered with EPA and are required to be labelled properly as to their toxicity to humans, their particular hazards, their routes (s) of exposure, and the precautions to be taken to avoid accident, injury, or damage. Application of these pesticides may only be performed in accordance with the precautions set forth on the label. Also, under the Clean Air Act (41 U.S.C. 1857 et seq.) and the National Ambient Air Quality Standards for Total Suspended Particulates, EPA is responsible for maintaining ambient air quality by preventing or controlling air pollution.

Under the proposed OSHA standard, the current permissible exposure limit (PEL) of 20 ppm would be reduced to .100 ppm as an 8-hour, time-weighted average (TWA), with a ceiling of 0.5 ppm. This reduction in the exposure limit is not anticipated to impact significantly on the external environment because (1) any resultant emissions to the external atmosphere would not represent a significant increase, (2) no solid waste is directly associated with EDB fumigation, and (3) the standard is not likely to impact upon the use of leaded gasoline, the largest outlet for EDB and related emissions. In addition, provisions of the proposal such as medical surveillance, employee information and training, hygiene facilities and practices, warning information, recordkeeping, and protective equipment and clothing are not anticipated to have a significant impact beyond the workplace.

Although the removal of increased amounts of EDB from the workplace air might seem to contribute to the pollution of ambient air surrounding EDB operations and applications, this is not anticipated because the amount of EDB that migrates to the external environment is not likely to increase. Many operations occur outdoors and controls that might be implemented under the proprosal probably would not change the amount of emissions to the atmosphere. In cases where worker exposure is reduced by the use of improved control methods, such as negative-pressure ventilation and purge systems in fumigation chambers, atmospheric emissions of EDB would remain constant, having an insignificant impact on the external environment. To further illustrate, in cases where exhaust emissions from fumigation chambers are controlled by extending the height of the stacks, the ground level concentrations, rather than the quantity of EDB would be reduced.

In cases where liquid EDB is transported or stored, there may be some potential for spills or leaks. Because of the nature of EDB, however, such occurrences would not be as a direct result of the proposal and would continue to come under the jurisdiction of EPA and DOT regulations. Although instances of waste disposal have not been presented to the record, such disposal would also be covered by EPA Resource Conservation and Recovery Act regulations (PL 94-580, 90 Stat 2795, Sec. 2001 *et seq.*) and transportation would be regulated by the Department of Transportation. The requirements of the proposed standard will not alter present methods for waste disposal, transportation, or cleanup of EDB.

Although the largest outlet for EDB is as a scavenger in leaded gasoline, the amount present is less than 0.1 percent by weight. Exposure levels are also low during service station operations and during the distribution, storage, or bulk handling of leaded motor fuel. For this reason, these activities are exempted from the proposal. Any impacts on the use of EDB in leaded gasoline are most likely to occur as a result of the

continued use and demand for lead-free gasoline and the low growth of overall gasoline consumption, not as a direct result of the proposal.

Based on this discussion and other information presented in this Notice, OSHA concludes that there will be no significant impact on the general quality of the human environment external to the workplace, particularly in terms of ambient air quality, water quality, or solid waste disposal. OSHA, of course, reserves the right to perform additional environmental analyses based on the information and comments received in response to this Notice.

VIII. Clearance of Information Collection Requirements

The collection of information requirements contained in the proposed rule have been submitted to the Office of Management and Budget (OMB) for review under section 3504 (h) of the Paperwork Reduction Act of 1980. These collection requirements are not effective until OMB approval has been obtained and the public notified to that effect through a technical amendment to this regulation. Comments on this matter are invited and should be directed to: Office of Information and Regulatory Affairs, Office of Management and Budget, Attention: Desk Officer for Labor, Room 3208, New Executive Office Building, Washington, D.C. 20503.

IX. Summary and Explanation of the Proposed Standard

The proposed requirements set forth in this proposal are those which, based upon all currently available data, the agency believes are necessary and appropriate to provide adequate protection to employees exposed to EDB. OSHA has considered all recommendations received in response to the ANPR as well as numerous reference works, journal articles and other data accumulated by OSHA since the initiation of this rulemaking. The following sections discuss the individual requirements of the proposed standard.

1. Section 1910.1048. Paragraph (a). Scope and Application

This proposed standard for ethylene dibromide (EDB) is applicable to all places of employment where EDB is produced, reacted, released, mixed, blended, packaged, repacked, stored, transported, handled or distributed.

This proposed regulation does not apply to the application of EDB as a pesticide. Section 4(b)(1) of the Occupational Safety and Health Act states "nothing in this Act shall apply to working conditions of employees with respect to which other federal agencies . . . exercise statutory authority to prescribe or enforce standards or regulations affecting occupational safety or health." The Environmental Protection Agency (EPA) currently regulates the use of EDB as a pesticide and the application process for fumigation of agricultural products. EPA's jurisdiction arises under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*). EPA's actions indirectly affect the working conditions of employees who apply EDB as a fumigant, thus OSHA is preempted from exercising jurisdiction over those applicators as provided by section 4(b)(1) of the OSH Act. OSHA will, however, exercise jurisdiction over occupational exposures which occur subsequent to or "downstream" from the application of EDB as a pesticide.

OSHA has reviewed EDB exposure sampling data for manufacturing, blending, formulation and fumigation operations and data submitted in response to the Advance Notice for Proposed Rulemaking (ANPR) for EDB. Responses to the ANPR have provided additional information about these operations and worker exposures. OSHA has decided that this standard should apply to all workplaces in maritime and general industry. This decision is based upon available exposure information as well as the general toxicity of this material.

The proposed standard also applies to those places of employment which handle materials or commodities which have been fumigated with EDB or products containing EDB since airborne concentrations of EDB result from offgassing of fumigated commodities.

Wholesale and retail food stores, automotive service stations and the distribution, storage or bulk handling of leaded fuel are not subject to the requirements of this proposed regulation. The proposal does not cover these places of employment because OSHA's evaluation of the exposure data in these industries indicates that the potential hazards addressed by the standard probably do not exist in these industries. In addition, no hazard of dermal exposure exists when handling fumigated citrus in food stores.

It should be noted that although OSHA is proposing to exempt the above discussed operations from the standard, these operations would still have to comply with the new PEL. This is consistent with good industrial hygiene practice. The agency does not contemplate that this will place any burden whatsoever on employers not covered by this proposed comprehensive standard because all available information indicates that these workplaces have exposures well below the proposed action level.

A. Wholesale or Retail Food Stores

Under certain circumstances fresh citrus shipped from one citrus growing region to another must be fumigated with EDB to prevent the propagation of certain pests. The pests and larvae are killed by exposing the citrus to very high airborne concentrations of EDB for a specified period of time. During this time the citrus and its cardboard packaging material absorb EDB. After fumigation the fruit begins desorbing (offgassing) EDB into the surrounding environment. This offgassing continues for the next several days, diminishing over time.

Most of the fumigated citrus comes from Florida and Texas and is sold in California. OSHA conducted environmental monitoring of fumigated citrus shipments from Texas to California and from Florida to California. Florida and Texas must also fumigate citrus shipped to Japan.

Air samples were taken during fumigation operations and during the transport, unloading and warehousing of the fumigated citrus in California.[3] The results of OSHA's environmental sampling indicate that by the time fumigated citrus has been transported to the warehouses or retail food stores for marketing, very little potential for exposure to EDB remains. Sampling results indicate that airborne levels of EDB in the warehouses before shipment to food stores are below 15 ppb. While OSHA did not continue to monitor downstream exposures in wholesale and retail food stores, the reduction in the levels during shipping indicate that environmental levels must be extremely low at these destinations.

The data therefore indicates that exposures in wholesale and retail food stores are well below the proposed action level. For this reason, OSHA has decided to exclude these industries from this proposed standard.

B. Service Stations

EDB is used as an additive in leaded gasoline. After blending the additive into the gasoline, the amount of EDB present is less than 0.1% by weight (Ex. 5-54). According to the American Petroleum Institute (API), 606,000 service station workers have potential for

[3] From November 1981 to March 1982 OSHA participated in a control technology assessment study conducted by Arthur D. Little, Inc. for the U.S. Department of Agriculture's Animal and Plant Health Inspection Service. OSHA conducted the environmental monitoring of airborne EDB for this study. Samples were taken at the fumigation station and in the trailer as the citrus was offgassing and transported to California.

exposure to EDB from leaded gasoline (Ex. 5–54). The results from full shift air sampling show that levels are very low, ranging from 0.03 ppb to 0.30 ppb. The highest individual sample reported was 1.8 ppb. Standard Oil stated that the average EDB concentrations measured at certain Amoco service stations were less than 0.005 mg/m³ (0.65 ppb) (Ex. 5–30). NIOH sampling results corroborate these figures. Samples collected at Cincinnati area service stations (which ranged in times between 71 to 210 minutes) were all below the 0.003 mg (0.0004 ppm) analytical limit of detection. Actual exposures may have been lower, however, limitations in the sampling and analytical methods used did not allow a more quantitative assessment. (NIOSH Memo, October 4, 1977). All of NIOSH's results were below OSHA's proposed PEL of 100 ppb.

Operations associated with leaded gasoline currently require stringent worker protection because of the toxic ingredient tetraethyl lead (TEL). These operations require the use of dermal protection from TEL under the general industry standard 29 CFR 1910.133 and 1910.1000.

California's Final General Statement and Summary of Opposition Testimony Concerning the EDB Standard (Ex. 7–8, Page C2) also indicates that exposure levels from service station operations are low, typically less than 7 ppb. The California standard exempts exposures from leaded gasoline from all provisions except the permissible exposure limit. All the available data indicates that airborne exposure levels are below the action level for service station attendants. The agency has therefore decided to exclude gasoline service stations from coverage under this proposed standard.

C. Distribution, Storage, or Bulk Handling of Leaded Gasoline

The agency decided to exclude from coverage that portion of the leaded fuel industry involved in the distribution, storage or bulk handling of leaded motor fuels as the available data demonstrate negligible exposure in this industry. These operations involve closed systems where the percentage of EDB by weight is 0.1%. After bending the EDB into the fuel, the need to control exposure to another toxic ingredient, tetraethyl lead (TEL) adequately keeps EDB exposure well below 130 ppb (Ex. 5–38). Examination of the data submitted indicates all sampling results were below OSHA's proposed action level. The API submitted sampling data for employees from one company engaged in terminal operations including loading and unloading of truck tankers. All air sample results were well below the proposed action level and in fact were less than 10 ppb (Ex. 5–54). While there may be a possibility of spills or accidental release of leaded gasoline vapors containing EDB in air due to the volume of material transported, concentrations of EDB in such instances would vary in proportion to the amount spilled. Since leaded gasoline also contains TEL, which has a greater acute toxicity, precautions must be taken to protect workers during clean up operations or emergency situations. The precautions required for TEL also would provide protection against any potential exposure to EDB.

2. Paragraph (b). Definitions

This section contains a list of definitions applicable to this section.

An "action level" of 0.05 parts per million (ppm) (50 parts per billion (ppb)) as an 8-hour time weighted average is provided in the proposal. The action level is the point at which certain provisions of the proposed standard must be instituted, such as medical surveillance. It provides a way of maximizing employee protection in those instances where exposures are possibly significant and minimizing employer obligations by defining the point below which no action is necessary. The broad scope of the proposal necessarily encompasses many employers whose employees are exposed to levels of EDB below the PEL. OSHA expects that this action level mechanism will greatly limit the number of workplaces covered by this proposed standard. For example, medical surveillance only has to be implemented for employees exposed to EDB at or above the action level for a total of 30 or more days per year. If an employer can demonstrate that an employee has not been exposed to this level for the required duration, the employer does not have to place that employee in a medical surveillance program. Thus, the action level concept provides an objective means of tailoring different sections of the standard for those employees who are at the greatest risk of developing an illness from exposure to EDB.

The statistical basis for determining the action level has been discussed in connection with several other OSHA health standards. In brief, although all measurements on a given day may fall below the permissible exposure limit, some possibility exists that on unmeasured days the employee's actual exposure may exceed the permissible limit. Where exposure measurements are above one-half the PEL, i.e. above the action level, the employer cannot reasonably be confident that the employee may not be overexposed on days when measurements are not taken (Leidel, N.S. et al. 1975). Therefore, requiring periodic employee exposure measurements to begin at the action level provides the employer with a reasonable degree of confidence in the results of the measurement program.

This proposed standard incorporates a more appropriate term for establishing a Short Term Exposure Limit (STEL). While OSHA has in many instances used the word "ceiling" to define a 15 minute average measurement, the ACGIH defines ceiling as "a concentration that should not be exceeded even instantaneously." Since most of the agency's airborne exposure limits were adopted from ACGIH's Threshold Limit Values, less confusion may exist if the definitions are similar. So, like the ACGIH, OSHA believes that a STEL is not a separate independent exposure limit, rather it supplements the time-weighted average (TWA) limit where there are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature. STELs are recommended only where toxic effects have been reported from high short term exposures in either humans or animals.

A definition of the term "emergency" is included in the proposed standard. For the purpose of the standard, emergencies are occurrences such as, but not limited to equipment failure, rupture of containers, or failure of control equipment which may result in an unexpected release of EDB. The standard imposes requirements to protect employees during emergency situations, such as pre-arranged emergency planning and medical surveillance.

Every spill or leak does not automatically constitute an emergency situation. The exposure to employees must be high and unexpected. Emergency situations include dermal exposures from a splash or leak.

3. Paragraph (c). Permissible Exposure Limit

OSHA is proposing to reduce the permissible exposure limit (PEL) to 0.1 ppm as a TWA with a short term exposure limit (STEL) of 0.5 ppm. This proposed PEL is based on the findings by OSHA that exposure to EDB at the current PEL presents a significant risk to employees and that the proposed standard will substantially reduce that risk.

In making a determination of significant risk, it is appropriate for OSHA to consider a number of different factors. The Supreme Court in the

Benzene decision provided some general guidance as to the process, stating that "while the agency must support its finding that a certain level of risk exists with substantial evidence, we recognize that its determination that a particular level of risk is 'significant' will be based largely on policy considerations" (448 U.S. at 655, 656 n.12). Consistent with rational policy judgment, OSHA has recently identified the following factors as being among those which should be considered: (1) The quality of the underlying data; (2) the reasonableness of the risk assessment; (3) the statistical significance of the findings; (4) the type of risk presented, and (5) the significance of the numerical risk relative to other risk factors (47 FR 15358, 15365, April 9, 1982). These factors have been evaluated with respect to the EDB risk assessment performed (see Section VI of this preamble).

OSHA has determined that exposure to EDB at the present standard of 20 ppm clearly poses a significant risk of material impairment to employees. Material impairment means employees contracting cancer, suffering adverse reproductive effects and other adverse effects such as liver and kidney damage due to exposure from EDB. The significance of this risk has already been informally acknowledged by some industries, who have reacted to the developing information regarding the potential health effects of EDB by voluntarily reducing the exposure of its employees.

Data received in response to the ANPR indicate that all the major producers maintain worker exposure levels at 0.5 ppm (TWA) or less. Section 6(b)(5) of the OSHA Act states "The Secretary . . . shall set the standard which must adequately assures on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life". The agency does not feel that the 0.5 ppm level will adequately protect employees and therefore proposes to establish a PEL at the 0.1 ppm level. Ethyl Corporation, which has the largest EDB production facility in the world, stated that its current internal exposure guideline is 0.1 ppm averaged over 8-hours. Under normal operations, engineering controls maintain the exposure of the EDB operator at less than 0.1 ppm. (Ex. 5–47) Conversely, formulation operations, while having exposures below the current 20 ppm 8-hour TWA, still have high employee exposures.

A short term exposure limit (STEL) may be necessary to provide adequate protection against possible reproductive effects from acute exposure for EDB exposed workers. OSHA recognizes that in some operations, relatively high excursions may be encountered by employees for short periods of time. The Brown risk assessment (Ex. 11) recommends that a short term exposure level of 0.5 ppm be established. OSHA supports this recommendation and has consequently proposed a STEL limit of 0.5 ppm. OSHA solicits comments on the establishment of a STEL limit for EDB.

OSHA has considered the economic and technological feasibility of the proposed PEL. Based on data provided by OSHA contractors and data submitted to the record in response to the ANPR OSHA believes that achieving compliance with a PEL of 0.1 ppm as an eight hour time-weighted average STEL and a of 0.5 ppm as averaged over a 15-minute period during the workday is both economically and technologically feasible. (See section VIII and the Regulatory Analysis for further discussion of this issue.)

4. Paragraph (d). Regulated Area

The proposal requires employers to establish a regulated area where airborne exposures to EDB are at or above the action level. Access to the regulated area is to be restricted to those persons required by their job duties to be present in the area; specifically, to those authorized entry by the employer, this proposal or the OSH Act.

The purpose of a regulated area is to ensure that employers make employees aware of the presence of EDB at levels approaching the PEL in the work place. This may be accomplished by posting a sign. The establishment of such a regulated area is an effective means of limiting the risk of exposure to as few employees as possible. This is consistent with good industrial hygiene practice when exposure to a toxic substance can cause serious chronic health effects. This requirement has other benefits in that where personal protective equipment (PPE) may be required in these areas, the additional obligations imposed by the proposal when PPE is used is also restricted to as few persons as possible.

Additional protective measures are necessary to restrict possible ingestion and absorption of EDB for workers within a regulated area. EDB is readily absorbed through the skin and can produce systemic toxicity. Therefore the agency proposal requires employers to prohibit workers from eating, smoking, drinking or applying cosmetics in regualted areas. This is designed to reduce the risk of inadvertent exposure to EDB via contaminated materials.

This section also requires that whenever an employer at a muti-employer worksite establishes a regulated area, that employer must communicate to other employers at the worksite the location of the regulated area and its access restrictions. Such extended communication would lessen the possibility of prohibited work practices and is intended to preclude inadvertent exposure of persons not involved in EDB related operations. OSHA believes that employers who have employee exposures to EDB at or above the action level have the responsibility to coordinate their work with all other employers whose employees may be exposed because of their proximity to the worksite. A specific method of communication is not required; this allows the employer the necessary flexibility to communicate the information to other employers at the work site in the most effective way possible.

OSHA is aware that under some circumstances regulated areas may need to be established in situations involving non-permanent worksites. For example the shipboard loading of fumigated commodities may result in airborne concentrations of EDB in the cargo holds in excess of the action level. In such instances the ship's hold would become a regulated area and access to and from it must be limited until such time as the EDB levles are reduced below the action level. A similar situation may arise at warehouse facilities during the time they house EDB fumigated commodities.

OSHA is cognizant of the problems presented by these temporary worksites and seeks comments regarding the establishment of such regulated areas.

5. Paragraph (e.) Exposure Monitoring

The monitoring requirements of the standard are proposed pursuant to section 6(b)(7) of the Act which mandates that standards dealing with toxic materials promulgated under section 6(b) shall, where appropriate, "provide for monitoring or measuring employee exposure at such locations and intervals, and in such manner as may be necessary for the protection of employees." The primary purpose of monitoring is to identify the sources of EDM emission and to determine the extent of employee exposure to EDB. It is particularly important with EDB since it is a colorless, odorless substance and has been shown to cause adverse health

effects at low doses. Once a determination is made that control of employee exposure to EDB is required, monitoring will enable the employer to select proper control methods and evaluate the effectiveness of the methods selected. Additionally, monitoring enables employers to notify employees when their exposure levels exceed permissible limits, as required by section 8(c)(3) of the Act. Such information is also necessary for the examining physician in order to effectively implement a medical surveillance program. For purposes of the monitoring requirements, as well as other provisions of the proposal, "exposure" means that which would result if respiratory protection were not used.

The proposed standard requires that exposure monitoring be conducted by taking air samples that are representative of each employee's full shift and short term exposure to EDB. The standard requires that for all operations, except those which are seasonal or intermittent, employers must conduct an initial monitoring within 60 days of the first introduction of EDB into the work area. however, if the intial monitoring or any subsequent monitoring indicates employee exposure to EDB above the action level but below the PEL, the employer than incurs an obligation to continue to perform monitoring. The employer must establish a cycle to repeat the monitoring of each such employee's exposure at least annually. A more frequent obligation occurs if employee exposure is found to be above the PEL. The proposed standard establishes a remonitoring cycle of at least every 6 months when exposure is found to be above the PEL.

In addition to the periods specified for remonitoring cycles, an employer must remonitor and make a new determination of employee exposure within 15 days (for other than seasonal exposures) if there has been a change in production, process or control measures which may result in new or additional employee exposure to EDB It is contemplated that the employer may use the periodic monitoring results to fulfill this additional monitoring requirement provided the periodic monitoring is done within 15 days of the change in production, process or control measures.

Employers can terminate the monitoring if employee exposure is found to be below the action level. However, if there is a reason to suspect that new or additional exposure may occur because of a change in production, process or control, the employer must reinstitute the monitoring program.

OSHA believes that it is necessary in those workplaces where EDB is present that each employer measure employee exposure to EDB using a reliable and accurate sampling method. Monitoring must at least be representative of each employee's full shift and short term exposure. Each employee's individual exposure need not be measured to fulfill the monitoring requirement, as long as sufficient sampling is done to allow the employer to determine each employee's exposure. This provides some the flexibility in complying with the intent of the initial monitoring requirement without incurring unnecessary costs from repetitive monitoring procedures.

The employer has the latitude of selecting the number of samples taken to represent full shift exposure for each job classification on each shift. For those job classifications with similar exposure on all shifts, only one set of representative measurements per job classification is necessary. This will minimize duplicative efforts and costs in complying with the monitoring requirements.

Although individual measurement may be the ultimate indicator of an employee's exposure, OSHA believes the requirement for individual measurement may be too burdensome. Moreover, representative measurements will adequately reflect exposure provided that representative samples include worst case exposure scenarios. Measurement of exposure need only be made once, assuming exposures are below the action level for continuous exposures. The determination need only be repeated if there is a change in operation such that it may create new or additional EDB exposure. The termination of the monitoring provision is only applicable to continuous operations below the action level so long as there is no change in production, process or control which could result in new or additional exposure.

Employers are not precluded from taking individual exposure measurements for each employee; individual measurements are certainly considered to be representative; however, representative monitoring requirements merely establish the minimum that the employer must meet. In establishments having more than one work operation involving the use of EDB, for monitoring to be representative, such monitoring must be performed for each type of employee exposure within each operation. Employers who have taken exposure measurements within six months of the effective date of the final regulation may use the results of those measurements, provided that they meet the accuracy and confidence levels delineated in paragraph (e)(5), to satisfy the requirements for conducting initial monitoring.

Certain uses of EDB are seasonal in nature as opposed to continuous, year-long operations. One such major noncontinuous use is the fumigation of citrus which is conducted after harvest but before the delivery of fruit to the warehouse. Other uses of EDB are intermittent in nature. An example of intermittent use would be the fumigation of grain in grain elevators or the arrival at elevators of freshly fumigated grain that may occur many times during the calendar year, albeit sporadically. A special definition of intermittent exposure is described in the methods of compliance section of this preamble.

Employers who have operations where employees are exposed to EDB on a seasonal or intermittent basis are required to conduct exposure monitoring while EDB is present in the workplace. Seasonal or intermittent operations may be extremely sporadic and variable; therefore, the proposal requires monitoring at least annually regardless of the results of the last monitoring event. The agency believes this is necessary to assure employee protection in view of the fact that it will be difficult to ascertain whether conditions and exposures remain the same from year to year. Accurate exposure measurements in these situations are further complicated because EDB is a colorless, odorless substance at the PEL.

Employers with seasonal operations are further required to conduct the monitoring within 30 days of start up or within 30 days of the first introduction of EDB into the workplace. The proposal does not allow a termination of monitoring for operations which are seasonal or intermittent for the reasons that it will be difficult to ascertain without remonitoring whether exposures are the same from year to year. No specific period of time is given for remonitoring after a change in operation under these circumstances because the exposures may be very short or sporadic and remonitoring may have to be done quickly to afford adequate protection to workers. OSHA is aware that seasonal and intermittent operations may have greater fluctuations in exposure than continuous operations. Due to EDB's extremely toxic properties and in view of these fluctuations, remonitoring must be conducted as soon as possible after the fluctuation.

OSHA believes employees have a fundamental right to be apprised of the results of monitoring whether or not

they are above the PEL. This is consistent with the mandate of section 8(c)(3) of the Act which not only requires that accurate employee exposure records be kept when monitoring is required but that employees be given access to such monitoring records.

Although 29 CFR 1910.20 requires that employees have access to exposure records upon request, the proposal requires that the employer notify all employees of the exposure measurements which are representative of their exposure. This explicit requirement to inform employees has educational value and will encourage more effective and enlightened worker participation in occupational health programs. Recognizing that for notification to be an effective informational process it must occur in a timely manner, the proposed standard requires an employer to notify each employee of his or her exposure within fifteen (15) days of obtaining the results of measurement. OSHA believes that 15 days is a reasonable period of time to implement this requirement.

The employer is given the flexibility to communicate monitoring results in a manner that is judged to be most reasonable. Only in those instances where an employee's exposure is above the PEL is the employer required to notify the employee of the results of monitoring in writing—stating that the PEL was exceeded and provide a description of any appropriate corrective action taken.

OSHA is aware that in some circumstances, particularly in those involving stevedoring operations, employees who are monitored for EDB exposure may not always work for the same employer or report to the same work location each day. Under these circumstances, it may be difficult to directly notify employees of their monitoring results. While OSHA fully expects the employer to make every reasonable attempt to notify those affected employees, the proposed regulation allows the employer to notify the employee's authorized representative of the monitoring results.

The available methodology for sampling and analysis of EDB demonstrates that it is possible to monitor employee exposures down to 0.001 parts per million. At these concentrations sampling and analytical methodologies are available which have an accuracy to a confidence level of 95 per cent, of not less than plus or minus 25 per cent.

Samples may be collected by absurption of EDB on charcoal contained in glass tubing through which a volume of air is drawn. Passive dosimeters may also be as effective in evaluating 8-hours exposures. The use of a portable gas chromatograph may be of special use in evaluating peak or short term exposure on site. The NIOSH analytical method (P&CAM 260) contained an Appendix D will detect EDB in parts per billion with the accuracy delineated in the proposal using gas chromatography and electron capture detection. Although these techniques require care, they are readily available and should pose no special difficulties for employers covered by this proposal.

The proposed standard allows personal sampling using charcoal tubes or other absorbent type measurement methods for monitoring. This type of sampling must be followed by a quantitative chemical analysis that usually occurs offsite some days later. Traditionally, OSHA has used this method to monitor employer compliance with its health regulations. However, this approach may be completely inappropriate for monitoring intermittent operations under changing conditions. For example, the results from monitoring stevedores loading holds in a ship, using charcoal tubes as a collection media, later followed by formal analysis in a chemical laboratory, probably would not be available until after the ship has left the dock and the workers have left the worksite.

A more appropriate and advantageous monitoring technique would be to require that only direct reading instruments be used in these situations. By direct reading, OSHA means some method of immediately being able to determine employee exposure levels. In this manner an employer would immediately know if the exposure levels are above the PEL and the employer could initiate action to reduce those levels. In addition, direct reading instruments would indicate when the level was exceeded so that other protective measures might be instituted. Another advantage of direct reading monitoring capability would be the ease of informing employees of their monitoring results while they are still at the worksite. An apparent disadvantage is the lack of readily available testing equipment. The only device OSHA is aware of that will conform to the precision and accuracy requirements of the proposed standard and selectively screen out other chemicals, is a gas chromatograph (GC). Portable GC's cost more money initially than pumps and charcoal tubes and require experienced professional operators to use.

The Florida Department of Citrus has had some experience in the use of a GC for monitoring exposure levels. OSHA requests comments and suggestions for monitoring seasonal and intermittent exposures and specifically requests comments on whether monitoring with direct reading instruments should be required.

6. Paragraph (f). Observation of Monitoring

Section 8(c)(3) of the Act requires that employers provide employees and their representatives with the opportunity to observe monitoring of employee exposures to toxic substances or harmful physical agents. In accordance with this section, the proposal contains provisions for such observation of monitoring for EDB exposures.

The observer, whether an employee or a designated representative, must be provided with, and required to wear, any personal protective equipment that is required to be worn by those working in the area that is being monitored. The observer must also comply with all other applicable safety and health procedures.

7. Paragraph (g). Methods of Compliance

The proposed standard requires that except for a narrowly defined exception discussed below, the employer must institute feasible engineering and work practice controls to reduce employee EDB exposures to or below the permissible exposure limit. Where engineering controls or work practices cannot be instituted to reduce exposure to or below the permissible level, these controls must nontheless be implemented to reduce exposures to the lowest feasible level. Where engineering controls do not reduce exposure below the PEL, they must be supplemented by the use of respirators to provide the necessary protection.

The proposed rule's reliance on engineering controls as the primary means of compliance is, in part, an acknowledgment that a particularly effective method of controlling employee exposure is to control the emission of toxic substances at their source through mechanical means combined with the use of work practices. Good engineering and work practice controls also minimize splashes and spills. An added benefit of these controls is reducing dermal exposure to employees.

However, OSHA also recognizes that respirators may provide acceptable protection when an employer establishes stringent procedures and then carefully supervises their implementation on a continuous basis. The agency recently published an ANPR (48 FR 7473) requesting comments on all

relevant issues related to the circumstances in which it might be appropriate for OSHA to allow greater reliance on respirators to protect workers from the various airborne contaminants regulated by OSHA. The agency is particularly interested, in conjunction with that regulatory initiative, in receiving comments, information and data concerning the extent to which respirators may provide effective protection against EDB exposure and may be relied upon as a substitute for engineering controls beyond those circumstances described in this proposal.

The engineering control requirements contained in this proposal may not be technologically or economically feasible in some operations. In recognizing these circumstances the proposal allows an employer to demonstrate the infeasibility of engineering and work practice controls in a particular operation and allows the use of respirators as supplementary protection in these circumstances. The burden of proof is appropriately placed on the employer to show that engineering and work practice controls are not feasible. The employer is familiar with the workplace operation and is therefore in the best position to evaluate various types of controls as they apply to that particular workplace environment. There are many types of engineering and work practice controls available to reduce exposure. For example, in a warehouse the use of specially equipped forklift trucks employing such technology as the use of a downdraft purified air flow may provide the protection necessary. Similarly, OSHA believes that the use of portable blowers on the decks of ships being loaded with EDB fumigated commodities may be extremely effective in reducing exposures. The potential technological problems and economic ramifications of installing various controls and implementing various practices may vary substantially from workplace to workplace.

In addition to permitting alternative compliance methods upon a showing that engineering and work practice controls are not feasible or have not been installed, this proposal allows the employer a measure of discretion in selecting the method of complying with the PEL in certain limited situations. Thus where an employer has a workplace where exposures to EDB are not only intermittent but are limited to a few days per year (30), the employer may select among alternative methods of compliance: engineering controls, work practice controls, respirator protection or any combination of these controls to comply with the PEL. OSHA is proposing to allow the use of these compliance alternatives where extremely sporadic and intermittent exposure patterns may make effective engineering controls and work practice controls impractical, disruptive and inconvenient. For the purpose of this proposal, intermittent operations are defined as those which result in exposures occurring for 1 or 2 days at any one time. A total of 30 days per year of workplace exposure is meant to describe days of operation involving the use of EDB in the workplace and not the number of days an employee is exposed. The agency has chosen to articulate this exposure as workplace exposure and not employee exposure to better characterize its intended application. The 30 day exemption provision is not intended to permit the use of employee rotation or short tenure employees in lieu of compliance with the general requirements of the standard.

The proposal also includes a provision requiring an employer who either creates or has control over abating a hazard to institute work practice controls to reduce EDB exposures to downstream employees of other employers. The requirement was added because in some situations the previous employer (i.e. a trucker or shipper) may be in the best situation to take action because that employer has both the knowledge of the hazard and ability to aid in the control of employee exposure. The provision is not intended to be difficult or burdensome to the employer who could affect potential exposures of downstream personnel to EDB. For example, a trucker may be able to reduce significantly exposures to employees unloading fumigated citrus by opening the rear doors of the trailer and aerating the load before unloading.

Administrative controls which distribute exposures over a large number of workers for less time are not permitted in lieu of engineering controls or limited respirator usage. The use of this control practice increases the population of employees at risk from exposure to EDB. Therefore, its use as a control strategy before the use of respiratory protection is not contained in this proposal.

OSHA requests comments on all aspects of the compliance approach taken in this proposal.

8. Paragraph (h). Respiratory Protection

The proposed standard requires that whenever respirators are necessary to reduce employee exposure to or below the PEL the employer must provide the respirators at no cost to the employee and assure their use. The use of respirators may be necessary to reduce employee exposure where the use of engineering controls or work practice controls are not feasible, as supplementary protection if such reduction controls will not achieve the necessary reduction while controls are being implemented and during emergency situations. In addition, the proposal gives the employer the option of using respiratory protection to control workplace exposures to EDB which are intermittent and less than 30 days per year.

The proposal contains specific requirements for the use, selection, maintenance, and fitting of respirators. The proposal contains a table listing the types of respiratory protection to be provided based on airborne concentrations of EDB in the workplace. The respirator selection table is consistent with the American National Standard Institute's Z-88.2—1980 practices for respirators protection factor table. The table is also similar to that recommended in the NIOSH Criteria Document, except that OSHA proposes to allow the use of negative pressure respirators under certain conditions. Historically, NIOSH has not recommended the use of negative pressure air-purifying respirators when the regulated substance has poor warning properties and cannot be detected by smell at concentrations which are half the PEL. EDB is considered to have poor warning properties; the odor threshold of EDB in 50% of the population tested is 10 ppm, which is one hundred times greater than the proposed PEL of 0.1 ppm. OSHA understands NIOSH's concern and their failure to approve negative pressure air-purifying respirators for materials which have poor warning properties. Since it is not possible for the respirator wearer to detect leakage or breakthrough within the facepiece until clearly overexposed, OSHA is proposing to allow the use of air-purifying negative pressure respirators under certain circumstances.

Generally, where negative pressure respirator use is allowed, OSHA requires that the respirator be approved by NIOSH/MSHA under the provisions of 30 CFR Part 11 for use with a particular substance or a class of substances. As noted above, NIOSH will not approve a negative pressure air-purifying respirator for use with substances with poor warning properties such as EDB. This proposal would allow their use at low concentrations where specified fit testing is done. In this instance where negative pressure air-purifying respirators are used, the

proposal requires that they must have NIOSH approval for use with organic vapors, a more general designation, rather than foregoing the approval requirements altogether. The NIOSH approval system helps assure the necessary quality control in the manufacturing of respirators and minimizes the manufacture and sale of poorly designed or inefficient respirators.

OSHA has determined that organic vapor cartridges can adequately absorb airborne concentrations of EDB up to 1 ppm. Organic vapor canisters can adequately absorb airborne EDB up to 10 ppm. OSHA has conducted limited tests of the collection efficiency of half-mask cartridge and full face organic vapor canisters for a few respirators produced by several manufacturers at concentrations above the proposed PEL (Nelson, 1983). The study tested cartridge and canister breakthrough of EDB under 85% relative humidity and demonstrated that the collection media was adequate to provide protection if the EDB concentration was maintained at or below the limits described in Table 1. As a result of this testing OSHA believes that cartridge charcoal filters can provide at least eight hours of protection form airborne concentrations of EDB up to 1 ppm and that canisters can provide protection for at least 16 hours without breakthrough for exposures of EDB up to 10 ppm. OSHA is proposing to allow the use of half mask cartridge respirators for up to 8-hours during a work shift (where the airborne EDB concentration is not greater than 1 ppm) and the use of full face canister respirators (where the airborne EDB concentration is not greater than 5 ppm) for two 8-hour work shifts within one 48 hour period on two consecutive days. The 48 hour limitation is necessary to protect the integrity of the absorbent material and to assure that the collection efficiency is not compromised by water, vapor or solvent migration.

Since EDB has poor warning properties and no end of service life indicators are available, cartridges and canisters must be properly tagged with information concerning when their use began. A label which indicates the date and time of a canister's installation in the respirator is required to assure it is not used beyond the period allowed by the proposal. Additional testing may reveal that the collection media could provide protection for a longer period of time. If additional canister or cartridge testing demonstrates that the absorption media can last longer, these data may support less frequent replacement of the cartridges or canisters. Additional test data concerning the proposed use of air-purifying respirators is requested.

Numerous other factors may affect the performance of air-purifying respirators. Proper fit of the respirator is critical. In this type of respirator negative pressure is created within the facepiece when the wearer breathes. This may result in workplace air entering the facepiece through gaps and leaks in the facepiece seal, instead of passing through the absorbent material. Obtaining a proper respirator fit may require the fit testing of a variety of different mask sized from several manufacturers to select the facepiece with the best fit (least leakage around the faceseal) for each employee.

Because of the exposure hazards that may occur if a proper faceseal is not obtained while using a negative pressure respirator and because of EDB's poor warning properties, the proposal requires qualitative or quantitative fit tests be conducted when negative pressure respirators are used. Either qualitative or quantitative fit tests are required at the time of initial fitting and at least annually thereafter. Therefore, procedures for conducting qualitative fit tests are contained in the mandatory Appendix A of this proposal.

Quantitative fit testing is a procedure whereby the level of penetration of a test agent of a known concentration is measured inside the facepiece of the respirator. Quantitative respirator fit testing is generally recognized as the ideal method for determining how well as repirator fits any one individual, in that it allows the employer to continue testing until the optimum or best fitting respirator is identified and selected for the employee. Quantitative fit testing requires the use of a sophisticated monitoring device and is more expensive than qualitative fit testing to perform. Moreover, quantitative fit programs have limited availability which minmizes their usefulness for many worksites. OSHA believes that while quantitative fit testing may be preferred, qualitative testing which is conducted in accordance with the protocols described in Appendix A accomplishes the intent of the standard to assure that each employee receives and wears the respirator which provides the greatest level of protection.

Qualitative fit testing is a technique whereby a person wearing a respirator is tested to see whether a test agent with a low odor threshold can be detected inside the respirator. Qualitative fit testing is a more subjective test than quantitative testing because it depends on the individuals ability to detect the test agent. The IAA test was not designed to determine protection factors greater than 10. Therefore, there is some question as to the adequacy of using the IAA qualitative fit test when employees are to be assigned to work in atmospheres of up to 100 times the PEL. OSHA solicits comments on whether this procedure, which has been proposed in Appendix A, is adequate to assure worker protection. Submissions recommending alternative fit test procedures are requested.

While OSHA has proposed that respirators may be used to reduce employee exposure, negative pressure air-purifying respirators may only be used in concentrations of EDB below 5 ppm. These respirators are more practical than those recommended by NIOSH, they are generally lighter than self-contained breathing apparatus (SCUBA) and allow greater employee mobility than airline respirators; both of these factors may lead to greater employee aceptance. In addition, negative pressure air purifying respirators are less expensive than the other respirators permitted for use with EDB. OSHA believes that with additional safeguards, such as careful qualitative fit testing, air purifying negative pressure respirators can be used as safely as other types of respirators and can provide adequate protection against EDB in the 1–5 ppm range even though EDB has poor warning properties.

Where employees are exposed to levels of EDB greater than 5 ppm and respirator usage is permitted, airline or positive pressure respirators must be used. Airline and similar positive pressure respirators use uncontaminated air and do not have the problems associated with exceeding the absorption media's capacity (which is the case with cartridges and canisters). OSHA is only allowing airline or SCBA's which operate in the positive pressure mode. Facepiece leakage is minimized with positive pressure respirators. Therefore they can be used in both high and low airborne concentrations of EDB. Employers can always use a respirator with a higher protection factor in lower concentrations of EDB.

All employees who are required to wear a respirator must be included in a medical surveillance program. This provision insures those individuals who will be exposed to EDB above the PEL regardless of the duration of exposure to be included in the medical surveillance program. In addition, respirator usage presents an excess burden to the pulmonary system of the employee. This

burden may result in symptoms such as shortness of breath, chest pain, dizziness or fatigue. All of these symptoms will be greatly exacerbated by pre-existing lung disease such as chronic bronchitis, emphysema, asthma or pneumoconiosis. It is, therefore, imperative that all employees who will be wearing respirators be medically screened to determine fitness for respirator usage. OSHA believes that the physician can best accomplish this through utilization of a physical examination, including a pulmonary function test and a chest x-ray.

The employee must be properly trained to wear the respirator, to know why the respirator is needed, and to understand the limitations of the respirator. An understanding of the hazard involved is necessary to enable employees to take steps for their own protection. The respiratory protection program implemented by the employer must conform to that set forth in 29 CFR 1910.134 which contains basic requirements for proper selection, use, cleaning and maintenance of respirators.

OSHA has determined that air-purifying respirators may be used in a rigidly controlled program of proper fitting and sorbent replacement. When the protection factors in the respirator table are followed, organic vapor cartridges and canisters may provide adequate protection for employees. OSHA has, in two other health regulations (vinyl chloride and acrylonitrile), allowed the use of negative pressure respirators for substances which exhibit poor warning properties.

The agency seeks comments on the use of respirators, the frequency of cartridge and canister replacement and the fit testing procedures.

9. Paragraph (i). Personal Protective Clothing and Equipment

The proposed standard requires that the employer provide and assure that employees who are subject to any possibility of skin contact with liquid EDB use all the appropriate resistant protective clothing and equipment necessary to prevent dermal exposure. Resistant clothing and equipment is that which does not allow EDB to penetrate through the material being worn for 480 minutes.

The agency does not contemplate that the protective clothing and equipment provisions of the proposed regulation would apply to those workplaces where the potential for dermal exposure to EDB results solely from the handling of materials or commodities fumigated with EDB. OSHA believes that the potential for dermal exposure to EDB while handling materials subsequent to fumigation is minimal and that special protective clothing would not be necessary.

The employer is to provide protective clothing, such as gloves, boots and neck coverings as necessary and appropriate to protect whatever portion of the body may come in contact with *liquid* EDB. The employer must also provide eye protection such as face shields, vented goggles or other protective equipment when necessary to protect against eye contact. The purpose of this provision is to protect the eyes against the burning and blistering effects of EDB liquid exposure. For those operations where employees enter confined spaces such as reactor vessels or storage tanks, EDB resistant full-body suits with supplied air hoods are required.

The proposal is sufficiently performance-oriented to allow the employer sufficient flexibility to provide only the protective equipment necessary to protect employees in each particular work operation from EDB exposure. Therefore, compliance can be tailored to fit the hazards posed on a day to day basis. Many operations may not require full body protective clothing, especially if very small amounts of EDB are being handled. However, the selection of the amount of protective clothing and equipment must be adequate to prevent any exposure to liquid EDB where skin or eye contact may occur.

The toxicity associated with dermal absorption of liquid EDB supports the required immediate removal of any nonresistant protective clothing or equipment and immediate drenching with water of all parts of the body which become wet with EDB or liquids containing EDB. Serious tissue degeneration can quickly occur from skin contact or dermal absorption. Suitable facilities for quick drenching or flushing of the eyes and body are required in all work areas for immediate emergency use. Emergency showers or quick drenching devices are needed in the immediate work area because EDB can cause burns or blistering of the skin within minutes after contact.

The regulation requires the employee to remove any clothing immediately after it becomes wet or damp with liquid EDB. In this context "immediately" means as soon as it is noticed by the employee; in other words an employee should not wait or take the time to proceed to the change room. This provision is necessary because of the extremely caustic nature of EDB and the acute absorption hazard it poses. The proposed standard also provides that EDB contaminated clothing and equipment must not be reworn until the EDB has been removed from the clothing or equipment. Protective clothing and equipment should not be worn or taken home after use because it could increase the number of people exposed to EDB. The proposed standard requires employers to replace protective clothing and equipment as necessary to assure its effectiveness but does not specify a given replacement interval. Employers should make frequent inspections of clothing to assure that it retains its effectiveness. A visual inspection means a systematic examination of the equipment to ensure such equipment is not leaking or developing leaks. This requirement is necessary to minimize exposure to employees. It is particularly necessary where, as here, the substance is a colorless, odorless and extremely toxic. Clothing and equipment contaminated with EDB or liquids containing EDB should not be worn into lunchrooms to prevent the contamination of eating areas and to minimize the potential exposure hazard to other workers.

As noted above under certain circumstances the proposed standard requires the use of EDB resistant clothing and equipment where there is a possibility of skin contact with liquid EDB. Only a few materials are capable of resisting the penetration of EDB through the material and subsequently to the skin. Viton (®) elastomer and polyvinyl alcohol (PVA) are two such materials (NIOSH 81-110, Stampfer, 1983). Polyvinyl alcohol can be used only in situations where EDB is not in solution with water. Water attacks the PVA and substantially decreases its effectiveness. In this situation, it must also be used in conjunction with another material to prevent contact with moisture from the skin. To assure adequate protection, the protective equipment provided must give 480 minutes or more of protection before breakthrough. Thus, when such EDB-resistant clothing becomes wet with EDB, there is no need for the employee to remove the clothing immediately because there is no likelihood of skin exposure.

The employer is required by the proposal to store all EDB contaminated protective clothing and equipment in containers bearing the following warning:

DANGER

(TRADE NAME)

CONTAINS ETHYLENE DIBROMIDE (EDB)

CANCER AND REPRODUCTIVE HAZARD

HARMFUL IF ABSORBED THROUGH SKIN

AVOID INHALATION AND SKIN CONTACT

These containers must be closed to prevent airborne exposure because liquid EDB can vaporize, increasing airborne exposure. OSHA believes that the regular cleaning, maintenance and replacement of protective clothing and equipment is necessary in order to protect against the hazards of dermal exposure. The proposal requires that the employer assures that employees remove protective clothing and equipment in the change room and that only those employees authorized to do so may remove contaminated clothing and equipment from the change room for the purpose of laundering, maintenance or disposal. This practice limits potential exposure to those specifically trained to handle contaminated materials.

Finally, the proposal requires that employers inform those who handle the contaminated protective clothing and equipment of the potentially harmful effects of EDB. This provision is designed to emphasize the need to use proper care in handling EDB contaminated protective clothing and equipment.

10. Paragraph (j). Hygiene Facilities and Practices

All employers covered by the proposal are required to assure that employees wash hands and face with soap and water prior to eating, drinking, smoking or applying cosmetics. The proposal specifies the hygiene facilities and practices required for employee protection in all other workplaces where employees are required to wear protective clothing to prevent skin or eye contact with EDB. The requirements of the rest of this paragraph do not apply to those workplaces where the potential for exposure to EDB results solely from the handling of materials or commodities fumigated with EDB. As noted above, OSHA believes that there is little potential for dermal exposure with liquid EDB while handling materials subsequent to the fumigation. Therefore, OSHA does not contemplate that this provision will provide any compliance burden where employee exposure results solely from the handling of materials or commodities fumigated with EDB.

The proposed standard requires that for all workplaces where employees are required to wear personal protective clothing, the employer provide shower and change room facilities for employees. Employees are required to take showers at the end of the workshift to minimize the potential for skin absorption as a result of EDB contamination of clothing.

11. Paragraph (k). Housekeeping

The proposed standard requires that where there are operations involving liquid EDB or liquids containing EDB, employers institute a program to detect leaks and spills which includes visual inspections. When leaks or spills of EDB are detected the proposal requires the employer to promptly repair all leaks and clean up all spills. These work practices aid in minimizing the number of employees exposed, as well as the extent of any potential for EDB exposure.

Prevention and removal of accumulations of liquid EDB on all surfaces are critically important aspects of minimizing employee exposure. The liquid if allowed to remain on the floor or work surfaces will slowly evaporate and contribute to a possible airborne hazard or it may become a dermal hazard through inadvertent skin contact. EDB's low vapor pressure which results in slow evaporation will contribute to and prolong the hazard. The requirement to clean up spills and drips refers to the prevention and removal of visible accumulations of liquid EDB on all surfaces.

Although this proposal does not contain a provision for lunchrooms, the agency has addressed the potential hazard of inadvertent ingestion of EDB contaminated materials. To minimize possible ingestion hazards, good hygiene is even more critical for employees who do not have lunchroom facilities. Therefore, employees are required to wash hands and face prior to eating and are prohibited from eating in regulated areas.

12. Paragraph (l). Emergency Procedures

OSHA believes that because of the chemical's highly reactive and destructive properties on major organs of the body, provisions addressing emergency situations are necessary to prevent harmful employee exposure to EDB. In the event of skin or eye contact with liquid EDB, the employer is required to assure that affected employees immediately wash or shower to reduce the danger of chemical burns and skin absorption. Emergencies are occurrences such as, but not limited to, equipment failure, rupture of containers or failure of control equipment which is likely to or do result in unexpected high exposures. The serious toxic effects of an acute EDB exposure hazard may not be immediately apparent to employees. Therefore, providing immediate medical attention to those employees exposed during an emergency is of paramount concern.

The appropriate procedures for dealing with emergency situations will vary among workplaces and operations. Employers must have a pre-arranged emergency plan; these pre-established plans are necessary because quick efficient actions during an EDB release are important to insure that a minimum number of employees are injured during emergency situations. Likewise such procedures may effectively reduce the extent to which any employee may be injured. The proposed standard therefore requires that at least the following be included: prearranged plans for immediate evacuation, transportation, and medical assistance for affected employees, designation of medical receiving facilities and names of physicians to contact, procedures for reentry, for clean up, decontamination and maintenance of areas when there is an EDB leak or spill and selection of appropriate clothing and equipment for personnel. This provision is necessary to assure that rescue and treatment is achieved in a timely and efficient manner. The proposed standard requires that any employees not necessary to correct the emergency situation, leave the area of the emergency. This restriction keeps the number of employees potentially exposed to EDB at a minimum. The follow-up procedures such as the requirement that PPE be furnished to employees for reentry and clean up, and that the collection of EDB waste be with an absorbent nonreactive material also decrease the potential for exposure. Because of EDB's properties and its offgassing potential, EDB contaminated waste, debris, containers or equipment are required to be disposed of in sealed labeled containers to prevent dispersion of EDB outside the container and protect those who subsequently handle this waste material during disposal.

13. Paragraph (m). Medical Surveillance

The proposed standard requires that each employer institute a medical surveillance program for all employees who are exposed at or above the level for 30 or more days per year or any employee who must wear a respirator regardless of the exposure duration. The medical surveillance program must be instituted prior to the employee's initial assignment to an area where the

exposure level will be at or above the action level for 30 or more days per year, or prior to the employee's wearing of a respirator regardless of the duration of the respirator usage and annually thereafter. Providing medical surveillance for employees who will be exposed at or above the action level for a total 30 days per year is consistent with other health standards promulgated by OSHA. Since some employees may be assigned to work areas where they will be exposed to EDB at or above the action level on a temporary or a short-term basis, OSHA has instituted a cut off period for the duration of exposure which triggers the medical surveillance program. As a result of the experience gained by OSHA's in the inorganic arsenic and coke oven proceeding, the agency has determined that this cut off period should be 30 exposure days per year.

In addition, OSHA is triggering the medical surveillance program for all employees who will be required to wear a respirator. The program must be instituted prior to the employee's actual wearing of a respirator and annually thereafter. The purpose of this provision is twofold. First, it allows those individuals who will be exposed above the PEL regardless of the duration of exposure to be included in the medical surveillance program. Second, respirator usage presents an excess burden to the pulmonary system of the employee. This burden may result in symptoms such as shortness of breath, chest pain, dizziness or fatigue. All of these symptoms will be greatly exacerbated by pre-existing lung disease such as chronic bronchitis, emphysema, asthma or pneumoconiosis. It is, therefore, imperative that all employees who will be wearing respirators be medically screened to determine fitness for respirator usage. OSHA believes that the physician can best accomplish this through utilization of physical examination, including a pulmonary function test and a chest X-ray.

EDB is a potential human carcinogen causing a variety of neoplasms including stomach, nasal, and lung cancers in experimental animals. EDB is also a potential human reproductive hazard causing pathological changes in sperm and testes as well as altering the fertility status in a variety of animal models. Additionally in humans, EDB has been shown to be a potent toxin affecting the liver, kidney, skin, and nervous system. Therefore, it is extremely important to incorporate a detailed medical surveillance program in the standard. This will allow the physician to identify any adverse health effects, or biological changes which may occur in workers exposed to EDB.

All examinations and procedures are required to be performed by or under the supervision of a licensed physician, without cost to the employee. While the physician will usually be selected by the employer, the proposed standard does not so mandate, leaving the employer free to institute alternative procedures such as joint selection with the employee or selection by the employee. Clearly, the appropriate person to conduct the medical examination is a licensed physician; however, certain parts of the required examination do not necessarily require a physician's expertise and may be conducted by another person under the supervision of the physician.

The proposed standard requires that the employer provide the examining physician with certain information. This includes: (1) A copy of the regulation and appendixes B and C, (2) a description of the employee's duties as related to exposure, (3) information regarding the use of personal protective equipment and (4) examination from previous work related medical exams not otherwise available to the physician. The purpose of making this information available to the physician is to aid in the evaluation of the employee's health in relation to assigned duties and determine fitness to wear personal protective equipment when required.

The medical surveillance program in the proposed standard includes a detailed work and medical history, complete physical examination including pertinent laboratory evaluation and assessment of pulmonary status (when required).

A complete work history including any past occupational exposure to chemicals or toxic substances is necessary in implementing an effective medical surveillance program. Information regarding such past occupational exposures may alert the physician to potential adverse health effects.

In conducting the medical history, the physician must inquire as to any medication that an employee is taking. Such information is important because studies have shown that some medication, specifically disulfiram (Antabuse®), may potentiate the carcinogenic effects of EDB. OSHA recognizes the sensitivity of such information and believes that if carefully written the examining physician's written opinion will safeguard physician-patient confidentiality. OSHA solicits comments and also seeks information regarding the possible adverse health effects of any other medication in conjunction with EDB exposure. The agency also solicits information as to whether the potentiating effects of Antabuse® with EDB are seen only with concurrent exposure.

The content of the physical examination is consistent with the identification of the adverse health effects that have been associated with exposure to EDB. It should emphasize the pulmonary, neurological, gastrointestinal, genito-urinary and dermal systems. In addition, a complete assessment of pulmonary status is mandatory when a respirator is required. This assessment is accomplished through a complete examination of the head, eyes, ears, nose, throat, thorax and lungs, in addition to a pulmonary function test and a chest x-ray (initially and at 5 year intervals). The frequency of chest X-rays was determined to avoid any potential health hazards associated with frequent radiographs and at the same time provide a sufficient time interval to identify any pathological changes which may have occurred. The purpose of the pulmonary function test which include a forced vital capacity (FVC), and forced expiratory volume at one second (FEV_1) is to assist the physician in making a determination as to whether the employee is capable of wearing a respirator.

The laboratory studies required by the proposal specifically address the biological changes that may occur with EDB exposure. These include a battery of blood tests performed to measure liver function (protein, albumin, alkaline phosphatase LDH, SGOT, SGPT, GGTP, and cholesterol) and kidney function calcium, phosphorus, BUN, uric acid, creatinine) and urinalysis.

The emergency medical surveillance provisions reflect OSHA's concern for those employees who, because of equipment breakdown, container rupture or other causes, may be exposed to higher doses of EDB. These workers may be at a relatively high risk of developing delayed systemic or dermal effects and are to receive immediate medical examination followed by a medical observation period of at least 72 hours. This medical observation period is critical in that the severe and sometimes fatal toxic effects of EDB often are not manifested at the time of exposure. Such observation should take place in a medical facility, preferably a hospital, where a licensed physician will be responsible for the personal supervision of all medical care delivery.

For each examination required under this section, the employer shall obtain a written opinion from the examining physician which shall include: (1) The physician's opinion as to whether the employee has any detected medical conditions or is taking any medication which would place the employee at increased risk of material impairment from exposure to EDB, (2) any recommended limitations on the employee's exposure to EDB or upon the use of personal protection equipment. This will include an opinion as to the employee's ability to wear a respirator when it is required, and (3) a statement that the employee has been informed by the physician of the results of the medical examination and any medical conditions resulting from EDB exposure which require further explanation or treatment.

The employer shall instruct the physician not to reveal in the written opinion given to the employer specific findings or diagnosis unrelated to occupational exposure to EDB. The employer shall provide a copy of the physician written opinion to the affected employee within 15 days of its receipt. The requirement that the employee be provided with a copy of the physician's written opinion will assure that the employee is informed of the results of the medical examination and may permit employees to take appropriate action. The purpose for requiring that specific findings or diagnosis unrelated to occupational exposure be excluded from the written opinion is to encourage employees to submit to medical examinations by removing the fear that employers may find out adverse or embarrassing information about their physical condition that may be unrelated to occupational exposures.

14. Paragraph (n). Employee Information and Training

The proposed standard requires the employer to provide a training program for employees who are exposed to EDB regardless of the level of exposure. The agency has decided it is necessary to train all exposed employees for the following reasons. OSHA believes that an information and training program is essential for the protection of employees, because employees can do much to protect themselves if informed of the nature of the hazards in the workplace. Data from the risk assessment indicates that there is still a risk of cancer, albeit a reduced risk, at the proposed PEL. In addition, EDB is highly absorptive through the skin. Skin contact with liquid EDB may increase an employee's exposure in an unquantified manner and may lead to serious health problems. Moreover, adverse reproductive effects may be linked to short term peaks. EDB is a corrosive material that may leak out of unsuitable containers. In view of the fact that the substance is colorless and odorless at levels that are many times greater than the PEL and the substance is harmful at extremely low exposure levels, employees should be trained in emergency procedures for handling EDB and should know what to look for because under some circumstances there may be unexpected and unnoticed exposures. Moreover, employees need to be informed about potentially increased risk of exposure to EDB that can result from the use of synergistic drugs, such as Antabuse®, even if exposures to EDB are low. To be effective, an employee education program must, at the minimum, apprise the employee of the specific hazards associated with the work environment. For this reason, the employer is required by the proposed standard to inform employees of the nature of EDB's potential health effects, the necessity for exposure control, safe work practices, emergency procedures; and the medical and industrial hygiene monitoring programs. Additionally, the training should be conducted relative to the employee's language and educational capability. The content of the training program is intended to apprise the employees of (1) the hazards to which they are exposed, (2) the necessary steps to protect themselves, including avoiding exposures, using respiratory protection and availing themselves of the opportunity for medical examinations, (3) their role in reducing exposure and (4) the contents of the standard.

The employer is required to provide to the Secretary and the Director, upon request, all materials relating to the training program. This is intended as an objective check of compliance with the training requirements as well as an indicator as to the adequacy of the contents of the program.

Training requirements imposed upon an employer with a constant workforce should not be too difficult to perform. Training a mobile or ever changing workforce such as truck drivers and stevedores may be very difficult. OSHA solicits comments concerning how and by whom this training can best be performed.

15. Paragraph (o). Warning Statements.

Section 6(b)(7) of the Act mandates that appropriate forms of warning be used to assure that employees are apprised of the hazards to which they are exposed in the course of their employment. OSHA believes that the control of safety and health problems involve the cooperation of employees, and the success of a safety and health program is highly dependent upon the employee's understanding of the hazards involved in the job.

OSHA believes, as a matter of policy, that employees should be given the opportunity to make informed decisions as to whether to work at a job under a particular set of working conditions. Before employees can make an informed decision to work in an area with potential hazards, the employees must be informed of any unsafe conditions. This is especially important for a mobile or temporary workforce. In addition, labels on materials or containers which leave the work area must be labeled to alert those who come in contact with such contaminated objects of the hazards of EDB. In light of the serious nature of the hazard of exposure to EDB, OSHA does not believe that periodic training alone will adequately apprise employees of the health hazards of EDB. However, OSHA believes that the requirement to post warning signs and affix warning labels when coupled with the training requirements discussed above will adequately inform employees. The use of warning signs and labels accomplishes both of these purposes as it alerts the employees to hazards and promotes safer work practices.

The proposed standard includes a requirement that warnings be affixed to all containers containing EDB or products containing EDB. The warning provisions of the proposed standard also require the employer to assure that warning signs, labels or stamps are affixed to any product containing EDB which leaves the employer's workplace. This requirement is designed to protect those employees outside the initial workplace who handle, transport or use this product. When an employer manufactures, formulates or sells a product containing a toxic substance, that employer's own employees and also the employees of other employers involved in handling, transporting, or using the product are exposed to that substance. This is especially true where the manufacturer, formulator or seller will, in many cases, be the only employer capable, through unique knowledge of the substance, of providing the information needed for protection of other employees. However, OSHA recognizes that other labels required by other regulatory bodies may satisfy the intent of this provision. Therefore, this proposal allows such labels to be used as substitutes if they contain the requisite information.

Due to the hazardous nature of EDB exposure, OSHA believes that emphasis should be placed on warning employees and other persons about the dangers of exposure. The proposed standard requires that warning signs be readable and not be obstructed or diminished in any way.

18. Paragraph (p). Recordkeeping

Section 8(c) of the Act requires that each employer shall keep and make available such records as the Secretary may prescribe as necessary or appropriate for the enforcement of this Act, or for developing information regarding occupational accidents and illnesses. The proposal would require employers to maintain written records of all exposure measurements, respirator fit test and medical surveillance.

The proposal requires that an exposure monitoring record be established for each employee or job classification. Such records are necessary to assist the effective evaluation and control of EDB. The record must contain a brief description of the work operation being sampled, the methods, dates and duration of sampling; and use of personal protective equipment.

Because symptoms of disease that may be related to exposure to EDB may not appear for years following an initial exposure, the proposal requires that records of employee exposure measurements be retained for at least 30 years. Medical records must be kept for at least the duration of employment plus 30 years which is consistent with 29 CFR 1910.20 access to medical records.

The proposal's recordkeeping provisions also require that the employee records be made available for examination and copying to the Secretary, the Director of NIOSH, employees, former employees or their designated representatives.

In addition, the proposal specifies that access to exposure and medical records by employees, designated representatives, and OSHA shall be accordance with 29 CFR 1910.20. Section 1910.20 is OSHA's recently promulgated generic standard for access to employee exposure and medical records (45 FR 35212). By its terms, it applies to records required by specific standards, such as this EDB standard, as well as to records which are voluntarily created by employers. In general, it provides for unrestricted employee and designated representative access to exposure records. Access to medical records is also provided for employees and, if the employee has given specific written consent, for the employee's designated representatives. OSHA retains unrestricted access to both kinds of records as well as respirator fit testing records, but its access to personally identifiable records is made subject to rules of agency practice and procedure concerning OSHA access to employee medical records, which have been published at 29 CFR 1913.10. An extensive discussion of the provisions and rationale for § 1910.20 may be found at 45 FR 35312; the discussion of § 1910.10 may be found at 45 FR 35384. It is noted that revisions to the access to records standard are being developed in an ongoing rulemaking proceeding (45 FR 35212). The proposed EDB standard may be affected by any changes which result from that rulemaking effort.

17. Paragraph (q). Effective Date

As proposed, all sections of the standard except paragraph (g) would become effective sixty (60) days following publication of the final rule in the Federal Register. This will give affected employers and employees time to familiarize themselves with the regulation and its content.

The engineering and work practice controls required by paragraph (g) shall be implemented as soon as possible but no later than 2 years from the date of the final standard's publication. This is to allow effected employers sufficient time to design and install necessary control equipment. The Agency also solicits information and supporting data on "start-up periods" and delayed implementation dates which may be necessary for other provisions of the standard.

X. Conclusion

OSHA recognizes that some gaps exist in the available scientific evidence concerning chronic effects on workers exposed to EDB. OSHA believes, however, that in this case we are dealing with a chemical that is a potential human carcinogen. The existence of unanswered questions cannot be permitted to delay the regulatory process of establishing a standard for protecting workers exposed to EDB. OSHA hopes that the public participation which is invited will help to fill whatever gaps may exist.

Therefore, based upon the available evidence and in view of the above considerations, OSHA believes that employee exposures to EDB must be reduced to the level of 0.1 ppm and that the other requirements to regulate exposure to EDB must be imposed as set forth in the proposal. OSHA will evaluate all the evidence received and entered it into the public record and issue a final standard based on the entire content of that record.

Comments and data are hereby requested in response to the specific questions posed in the discussion above. In addition, interested persons are invited to submit any other relevant comments and data on any of the provisions contained in the proposal.

XI. Public Participation

Interested persons are invited to comment on the proposed standard on or before November 21, 1983. Written data, views and arguments concerning the proposal must be submitted in quadruplicate to the Docket Officer, Docket H-111, U.S. Department of Labor, Room N-3620, 200 Constitution Avenue, NW., Washington, D.C. 20210 (Telephone 202/523-8076). Written submissions must clearly identify the provisions of the proposal addressed and the position taken with respect to each such provision. The data, views and argument will be available for public inspection and copying at the above address. All written submissions received will be made a part of the record.

Pursuant to 29 CFR 1911.11 (b) and (c), interested persons may in addition to filing written comments as provided above, file objections to the proposal and request an informal hearing with respect thereto, in accordance with the following conditions:

1. The objections must be postmarked on or before November 21, 1983;

3. The objectives must specify with particularity the provision of the proposed rule to which objection is taken and must state the grounds therefor;

4. Each objection must be separately stated and numbered; and

5. The objections must be accompanied by a detail summary of the evidance proposed to be adduced of the requested hearing.

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Authority

This notice was prepared under the direction of Thorne G. Auchter, Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, 200 Constitution Avenue, NW., Washington, D.C. 20210.

Pursuant to sections 6(b) and 8 of the Occupational Safety and Health Act [29 U.S.C. 655, 657], is hereby proposed to amend Part 1910 of 29 CFR by adding new § 1910.1048 as set forth below and deleting the entry "20 ppm" TWA, "30 ppm" acceptable ceiling concentration and "50 ppm" acceptable maximum peak and "5 minute" maximum duration from the ethylene dibromide listing in Table Z–2 of section 1910.1000, and inserting "0.1 ppm" in the TWA column and "0.5 ppm" in the acceptable ceiling column for the ethylene dibromide entry in Table Z–2 of § 1910.1000.

In addition, pursuant to section 4(b)(2) of the Act, OSHA has determined that this new standard would be more effective than the corresponding standards now in Subpart B of Part 1910, and in Parts 1915 and 1918, of Title 29, Code of Federal Regulations. Therefore, these corresponding standards would be pre-empted by this new § 1910.1048. This determination, and the application of new standard to the maritime industry, would be implemented by adding a new paragraph (i) to § 1910.19.

List of Subjects in 29 CFR Part 1910

Ethylene dibromide, Chemicals, Cancer, Health, Health records, Occupational safety and health, Respiratory protection, Risk assessment, Signs and symbols.

(Secs. 4, 6 and 8, of the Occupational Safety and Health Act of 1970 (29 U.S.C. 653, 655, 657); Secretary of Labor's Order No. 9–83 (48 FR 35736); (29 CFR Part 1911))

Signed at Washington, D.C., this 3rd day of October 1983.

Thorne G. Auchter,

Assistant Secretary of Labor.

XII. Proposed Standards and Appendices

Part 1910 of Title 29 of the Code of Federal Regulations is proposed to be amended as follows:

1. By adding a new paragraph (h) to § 1910.19 to read as follows:

§ 1910.19 Special provisions for air contaminants.

* * * * *

(h) *Ethylene dibromide.* Section 1910.1048 shall apply to the exposure of

everyone employee to ethylene dibromide in every employment and place of employment covered by §§ 1910.13, 1910.14, 1910.15, or 1910.16, in lieu of any different standard on exposure to ethylene dibromide which would otherwise be applicable by virtue of those sections.

§ 1910.1000 [Amended]

2. By removing the entry "20 ppm" TWA, "30 ppm" acceptable ceiling concentration and "50 ppm" acceptable maximum peak and "5 minute" maximum duration from the ethylene dibromide listing in Table Z-2 of § 1910.1000 and inserting "0.1 ppm" in the TWA column and "0.5 ppm" in the acceptable ceiling concentration column for the ethylene dibromide entry in Table Z-2 of § 1910.1000.

3. By adding a new § 1910.1048 to read as follows:

§ 1910.1048 1,2 Dibromoethane (ethylene dibromide).

(a) *Scope and Application.* (1) This section applies to each place of employment which is involved in the production, reaction, release, mixing, blending, packaging, repackaging, storage, transportation, handling, distribution and use of ethylene dibromide (EDB) or products containing EDB.

(2) This section also applies to each place of employment where exposure to EDB may result from: (i) Off-gassing of fruit, vegetables, grain or packaging materials fumigated with EDB; and

(ii) The spot fumigation of milling machinery and fumigation of grain products.

(3) This section does not apply to (i) The application of EDB as a pesticide under the regulations of the Environmental Protection Agency (40 CFR Part 162);

(ii) Wholesale or retail food stores;

(iii) Automotive service stations; or

(iv) The distribution, storage, or bulk handling of leaded fuel.

(b) *Definitions.* (1) "Action level," means employee exposure to an airborne concentration of 0.05 parts EDB per million parts of air (ppm) [50 parts per billion (ppb)] averaged over an 8-hour period (TWA).

(2) "Assistant Secretary," means the Assistant Secretary of Labor for Occupational Safety and Health, or designee.

(3) "Authorized person," means any person required by work duties to be present in regulated areas and authorized to do so by the employer, by this section, or by the OSH Act of 1970.

(4) "Clean change room," means an uncontaminated room separate from the work environment where employees put on clean clothing or protective equipment.

(5) "Container," means any receptacle, excluding pipes and piping systems, in which EDB or a liquid containing EDB is placed or kept, including reaction vessels, storage tanks and blending tanks.

(6) "Decontamination," means treatment of EDB contaminated materials by water washdown, ventilation, or other means, to assure that the contaminated materials will not expose employees to skin contact with EDB.

(7) "Director," means the Director, National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services, or designee.

(8) "Emergency," means any occurrence such as, but not limited to equipment failure, rupture of containers, or failure of control equipment which may result in an unexpected release of EDB or liquid containing EDB.

(9) "Employee exposure," means the exposure to EDB which would occur if the employee were not using a respirator.

(10) "Ethylene dibromide," ($C_2H_4Br_2$) (CAS Registry Number 106-93-4), means 1,2 dibromoethane (EDB) or a mixture of liquids containing EDB.

(11) "Intermittent operation," means those operations which result in exposures occurring for 1 or 2 days at any one time.

(12) "Offgassing," means the release of EDB vapors from materials or commodities previously in contact with EDB.

(13) "Regulated area," means an area where entry and exit is restricted to authorized persons.

(14) "Resistant clothing and equipment," means clothing, including gloves, aprons or boots made of materials which exhibit EDB breakthough times of greater than 480 minutes.

(15) "Short Term Exposure Limit (STEL)," means an airborne concentration to which workers exposed continuously for a short period of time cannot be exceeded. A STEL is defined as a 15-minute time-weighted average exposure which shall not be exceeded at any one time during a work day even if the 8-hour time weighted average is within the PEL.

(16) "Work practice procedures," means a written standard operating procedure by which an employee is trained to perform a task in a specific manner in order to minimize exposure.

(c) *Permissible Exposure Limit (PEL).* (1) Inhalation. (i) Time Weighted Average (TWA). The employer shall assure that no employee is exposed to an airborne concentration of EDB in excess of 0.1 parts per million parts of air (ppm) [100 parts per billion (ppb)] as an 8-hour time-weighted average;

(ii) Short Term Exposure Limit (STEL). The employer shall assure that no employee is exposed to an airborne concentration of EDB in excess of 0.5 parts per million parts of air (ppm) [500 parts per billion (ppb)] as average over any 15-minute period during the work shift.

(2) Dermal exposure. The employer shall take adequate precautions to insure that no employee is exposed to skin or eye contact with EDB.

(d) *Regulated Areas.* (1) The employer shall establish a regulated area whenever the airborne concentration of EDB is at or above the action level.

(2) Access to regulated areas shall be limited to authorized persons.

(3) The employer shall assure that employees do not eat, smoke, drink or apply cosmetics in a regulated area.

(4) The employer shall post regulated areas with signs containing the following information:

DANGER, [TRADE NAME] CONTAINS ETHYLENE DIBROMIDE (EDB) CANCER AND REPRODUCTIVE HAZARD. AUTHORIZED PERSONNEL ONLY. RESPIRATOR MAY BE REQUIRED

(5) Whenever an employer at a multi-employer worksite establishes a regulated area, that employer shall communicate to other employers at that worksite the location and access restrictions to the regulated area.

(e) *Exposure Monitoring.* (1) General. Each employer who has a workplace covered by this standard, shall measure and accurately determine employee exposure to EDB. Determination of airborne exposure levels shall be made from air samples that are representative of each employee's full shift and short term exposure to airborne EDB.

(2) Seasonal and Intermittent Exposures. (i) At least annually, each employer who has a work operation covered by this standard shall monitor employee exposure to accurately determine the airborne concentration of EDB to which employees may be exposed.

(A) For exposures during seasonal operations, initial monitoring shall be performed within 30 days of the startup or the first introduction of EDB into a work area.

(B) For intermittent exposures, the initital monitoring shall be performed within 30 days of the introduction of

EDB into the work area even if exposures are not daily.

(ii) If the monitoring required by this section reveals employee exposures to be in excess of the PEL, the employer shall repeat measurements of samples representative of each such employee's exposure at least every six months.

(iii) The employer shall promptly monitor and redetermine employee exposure whenever there has been a production, process or control change which may result in new or additional exposure to EDB or whenever the employer has any reason to suspect new or additional EDB exposure.

(3) Other Exposures. (i) Initial Monitoring.

(A) Each employer who has a work operation covered by this standard shall monitor employee exposures to EDB to determine whether any employees are exposed to EDB at or above the action level.

(b) Initial exposure monitoring shall be done within 60 days of an employer's first introduction of EDB into the work area.

(ii) Frequency of monitoring.

(A) If any monitoring reveals employee exposure to be above the action level but below the PEL, the employer shall repeat measurements of samples representative of each such employee's exposure at least annually.

(B) If any monitoring reveals employee exposures to be in excess of the PEL, the employers shall repeat measurements of samples representative of each such employee's exposure at least every six months.

(C) The employer shall remonitor and redetermine employee exposure within 15 days of any change in production, process, or control measures which may result in new or additional employee exposure to EDB.

(iii) Termination of monitoring. If the monitoring reveals employee exposure to be below the action level, the measurements need not be repeated except where there has been a production, process or control change which may result in new or additional exposure to EDB.

(4) Employee Notification. (i) Within 15 working days after the receipt of exposure monitoring results, the employer shall notify each employee of the monitoring results which represent that employee's exposure to EDB.

(ii) Whenever monitoring results indicate that employee exposure exceeds the PEL, the employer shall assure that each such employee receives a written notice informing the employee of the monitoring results along with a statement that the PEL was exceeded and a description of any corrective action being taken to reduce exposure to or below the PEL.

(iii) Where employees do not always report to the same work location, such as in stevedoring, and the employer is unable to notify the employee directly of the monitoring results, the employer shall provide the results of the exposure monitoring to the employee's authorized representative for distribution to affected employees.

(5) Accuracy of Measurement: The employer shall use a method of measurement which has an accuracy (with a confidence level of 95 percent) of not less than plus or minus 25 percent for concentrations of EDB at the action level.

(f) *Observation of monitoring.* (1) The employer shall provide affected employees or their designated representatives an opportunity to observe any monitoring of employee exposure to EDB required by this standard.

(2) When observation of the monitoring of employee exposure to EDB requires entry into an area where the use of protective clothing or equipment is required, the observer shall be provided with and be required to use such clothing and equipment and shall comply with all other applicable safety and health procedures.

(g) *Methods of Compliance.* (1) General. (i) The employer shall institute engineering and work practice controls to reduce and maintain employee exposures to EDB at or below the PEL, except to the extent that the employer establishes that such controls are not feasible. Where work practice controls are sufficient to accomplish this goal alone, engineering controls need not be implemented.

(ii) Where engineering and work practice controls are not sufficient to reduce exposures to or below the PEL, they shall nonetheless be used to reduce exposures to the lowest levels achievable by these controls and shall be supplemented by the use of respirators in accordance with paragraph (h) of this section. Respiratory protection may be instituted prior to the imposition of employee rotation as a control strategy.

(iii) Exception: Where exposure to EDB in a workplace is intermittent and occurs less than a total of 30 days per year the employer may use engineering controls, work practice controls or respiratory protection to reduce employee exposure to EDB in the workplace to or below the PEL.

(2) Specific. Employers shall institute work practice controls (such as aerating or venting of truck trailers or chimney stacking cartons) whenever feasible to reduce exposure to EDB of the first line receivers of fumigated commodities to or below the PEL.

(h) *Respiratory Protection.* (1) General. Where respiratory protection is required, the employer shall provide at no cost to the employee and assure the use of respirators which comply with the requirements of this paragraph to reduce employee exposures to or below the PEL.

(2) Respirators shall be used in the following circumstances: (i) In work situations in which engineering and work practice controls are not feasible to reduce exposures to or below the PEL; and

TABLE 1—RESPIRATORY PROTECTION FOR EDB

Concentrations of airborne EDB or condition of use	Respirator type [1]
(A) Not greater than 1.0 ppm. (1000 ppb).	1. A half mask or full face air-purifying respirator equipped with an organic vapor pesticide cartridge or canister; 2. Any supplied air respirator; or 3. Any self-contained breathing apparatus.
(B) Not greater than 5.0 ppm. (5000 ppb).	1. A full face air-purifying respirator equipped with an organic vapor or pesticide canister; 2. Any supplied-air respirator with full facepiece, helmet, or hood; or 3. Any self-contained breathing apparatus with full facepiece.
(C) Not greater than 100 ppm. (100,000 ppb).	A Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure mode, or with full facepiece, helmet, or hood operated in continuous flow mode.
(D) Greater than 100 ppm or entry and escape from unknown concentrations.	1. A combination respirator which includes a Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure or continuous flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or positive pressure mode; or 2. A self-contained breathing apparatus with full facepiece operated in pressure-demand mode. 3. Supplied-air suits may be necessary.
(E) Firefighting	A self-contained breathing apparatus with full facepiece operated in pressure-demand mode.

[1] Respirators specified for higher concentrations can be used for lower concentrations of EDB.

(ii) During the time period necessary to install or implement feasible engineering and work practice controls; and

(iii) Where workplace exposures to EDB are intermittent and EDB is used within the workplace less than a total of 30 days per year and engineering and work practice controls are not used to reduce exposure; and

(iv) In emergencies;

(2) Respirator Selection. (i) Where respiratory protection is required or

used to comply with this section, the employer shall select and assure that employees use the appropriate respirator in accordance with Table 1.

(ii) The employer shall select respirators from among those approved for use with organic vapors or pesticides by the National Institute for Occupational Safety and Health (NIOSH) under 30 CFR Part 11.

(3) Respirator Program. The employer shall institute a respiratory protection program in accordance with 29 CFR 1910.134 (b), (d), (e), and (f). Compliance with 1910.134(b)(10) shall consist of those specifications outlined in the medical surveillance section of this standard.

(4) Respirator Usage. (i) The employer shall perform and record the results of either quantitative or qualitative fit tests at the time of initial fitting and at least annually thereafter for each employee wearing a negative pressure respirator. The test shall be used to select a respirator facepiece which exhibits minimum leakage and provides the required protection as prescribed in Table 1.

(ii) The employer shall follow the test procedures outlined in Appendix A of this regulation when performing qualitative fit tests.

(iii) Where air-purifying chemical cartridge respirators are used, the air purifying cartridges shall be replaced at the completion of each shift.

(iv) Where air-purifying canister type respirators are used, the air-purifying canister shall be replaced at the completion of two work shifts within one 48-hour period. A label shall be attached to the canister to indicate the date and time at which it was first installed on the respirator.

(v) Employees who wear respirators shall be permitted to leave work areas to wash their face and respirator facepiece whenever necessary to prevent skin irritation associated with respirator usage.

(i) *Protective Clothing and Equipment.* (1) Provision and Use. Where there is the possibility of eye or skin contact with EDB or liquids containing EDB: (i) The employer shall provide at no cost to the employee and assure that the employee uses appropriate resistant clothing and equipment to protect the area of the body which may come into contact with liquid EDB such as:

(A) Full body protective clothing;

(B) Gloves, boots, head and neck coverings;

(C) Face shields, vented goggles, or other protective equipment;

(ii) Resistant clothing (suits) and supplied-air hoods shall be worn when entering confined spaces, such as storage tanks or reactor vessels.

(iii) All personal protective equipment provided shall comply with the provisions of 29 CFR 1910.132 and 1910.133.

(iv) Quick drench showers and eye wash fountains shall be provided within the work area for immediate emergency use.

(2) Removal and Storage. (i) Where resistant protective clothing is required it shall be removed at the end of each work shift and shall not be reworn until it has been decontaminated.

(ii) EDB-contaminated clothing and protective devices shall be stored, until they are decontaminated, in closed containers bearing a warning which contains the following information:

DANGER: (TRADE NAME) CONTAINS ETHYLENE DIBROMIDE (EDB); CANCER AND REPRODUCTIVE HAZARD; AVOID INHALATION AND SKIN CONTACT

(iii) The employer shall assure that no employee takes home EDB contaminated work clothing or equipment.

(3) Cleaning and Replacement. (i) The employer shall clean, launder, repair, or replace all required protective clothing and equipment for each affected employee as necessary to assure its effectiveness.

(ii) The employer shall assure that only trained persons remove protective clothing and equipment from the storage containers for the purpose of laundering, maintenance, or disposal.

(iii) The employer shall inform any person who launders or cleans EDB-contaminated protective clothing or equipment of the potentially harmful effects of EDB.

(j) *Hygiene Facilities and Practices.* (1) The employer shall assure that exposed employees wash hands and face with soap and water prior to eating, drinking, smoking or applying of cosmetics.

(2) Where employees are required to wear protective clothing to prevent skin or eye contact with EBD, clean change rooms and shower facilities, as described in 29 CFR 1910.141 shall be furnished by the employer for use by affected employees. The clean change room shall be contiguous to and have an entry from a shower room.

(3) The employer shall assure that employees wearing protective clothing or equipment to protect against skin contact with liquid EDB shower at the end of the work shift.

(k) *Housekeeping.* (1) All surfaces shall be maintained free of drips or spills of EDB.

(2) The employer shall institute a program for detecting leaks and spills including regular visual inspections of operations involving liquid EDB.

(3) All leaks shall be repaired and spills cleaned up promptly.

(l) *Emergency Procedures.* (1) In all work areas where EDB is present, the employer shall take all necessary steps to ensure that employees are instructed in and follow specific written emergency procedures appropriate for each operation or process which have been developed by the employer.

(2) The written emergency procedures shall include: (i) Prearranged plans for immediate evacuation, transportation, and medical assistance for affected employees;

(ii) Designation of medical receiving facilities and names of physicians to contact in the event of an EDB emergency;

(iii) Reentry procedures for cleanup, or maintenance into areas where EDB leaks or spills have occurred; and

(iv) Selection of the appropriate personal protective equipment and clothing which shall be used by trained personnel during an emergency.

(3) In the event of skin or eye contact with liquid EDB the employer shall assure that affected employees immediately wash or shower to minimize the danger of skin absorption.

(4) The employer shall require that employees immediately remove any nonresistant clothing which becomes wet with EDB or liquids containing EDB. Such clothing shall be stored in closed containers and shall not be reworn until it has been decontaminated.

(5) All employees, except those designated to correct the situation, shall be evacuated from the area where the emergency occurred until cleanup has been completed.

(6) Personnel reentering the spill or leak area shall be furnished with appropriate personal protective equipment.

(7) Any spilled or leaked EDB shall be collected by using vermiculite, dry sand, earth or other nonreactive material.

(8) EDB contaminated waste and debris shall be disposed of in sealed containers which prevent dispersion of EDB outside the container. (i) Such containers shall bear a warning containing the following information:

DANGER (TRADE NAME) CONTAINS ETHYLENE DIBROMIDE (EDB) CANCER AND REPRODUCTIVE HAZARD AVOID INHALATION AND SKIN CONTACT

(ii) Spent or leaking containers shall be promptly removed from the workpiece.

(m) *Medical Surveillance.* (1) General. (i) The employer shall make available a medical surveillance program for any employee required to wear a respirator or any employee exposed to EDB at or above the action level for a total of 30 or more days per year.

(ii) All medical examinations and procedures shall be performed by or under the supervision of a licensed physician, and shall be provided without cost to the employee, without loss of pay and at a reasonable time and place.

(2) Frequency and content. Before an employee can wear a respirator or at the time of initial assignment to an area where the employee is likely to be exposed at or above the action level for 30 days or more per year and at least annually thereafter, the employer shall provide that employee a medical examination. The medical examination shall include the following:

(i) A comprehensive work history with inquiry directed toward previous work-related exposure to toxic substances.

(ii) A comprehensive medical history with special emphasis directed to disorders of the liver, kidney, lungs and reproductive system.

(iii) A comprehensive physical examination, with particular emphasis given to the cardiovascular, pulmonary, neurologic, hepatic, renal and dermal system.

(iv) Laboratory examinations: Blood serum chemistry studies including, calcium, phosphorus, glucose, blood urea nitrogen, serum creatinine, uric acid, cholesterol, total protein, albumin, alkaline phosphatase, LDH, SGOT, SGPT, and GGTP; urinalysis,

(v) A chest X-ray, initially and at five year intervals, unless indicated more frequently by the examining physician, and a pulmonary function test, including FVC and FEV_1, if an employee is to wear a respirator; and

(vi) Any other test deemed appropriate by the examining physician after review of the above medical information.

(3) Special Examinations. If an employee is exposed to EDB in an emergency situation or develops signs or symptoms commonly associated with EDB exposure, the employer shall immediately provide the employee with a medical examination. This examination shall include those elements considered appropriate by the examining physician, and a 72-hour medical observation period to assure that the unexpected delayed systemic effects associated with acute exposure are minimized.

(4) Information provided to the physician. The employer shall provide the following information to the examining physician:

(i) A copy of this regulation and appendices B and C;

(ii) A description of the affected employee's duties as they relate to the employee's exposure to EDB;

(iii) The level of EDB to which the employee is exposed;

(iv) A description of any personal protective equipment used; and

(v) Information from previous employment-related medical examinations of the affected employee which is not otherwise available to the examining physician.

(5) Physician's written opinion. (i) For each examination required under this section, the employer shall obtain a written opinion from the examining physician which shall include:

(A) The physician's opinion as to whether the employee has any detected medical conditions or is taking any medication which would place the employee at increased risk of material impairment from exposure to EDB;

(B) Any recommended limitation on the employee's exposure to EDB or upon the use of personal protective equipment. This shall include an opinion as to the employee's ability to wear a respirator; and

(C) A statement that the employee has been informed by the physician of the results of the medical examination and any medical conditions resulting from EDB exposure which require further explanation or treatment.

(ii) The employer shall instruct the physician not to reveal in the written opinion given to the employer specific findings or diagnosis unrelated to occupational exposure.

(iii) The employer shall provide a copy of the physician's written opinion to the affected employee within 15 days of its receipt.

(n) *Employee Information and Training.* (1) The employer shall assure that all employees who are assigned to workplaces covered by this standard participate in a training program.

(2) Training shall be provided prior to or at the time of initial assignment and at least annually thereafter.

(3) The training program shall be conducted in a manner which the employee is able to understand and shall include: (i) A copy of this regulation and discussion of its contents and Appendix B;

(ii) The potential health effects associated with exposure to EDB with emphasis on the potential for serious internal injury before experiencing overt symptoms;

(iii) Instructions to immediately report to the employer the development of signs or symptoms of EDB exposure;

(iv) The safe work practices appropriate to each job with EDB exposure;

(v) The purpose for, proper use and limitations of personal protective clothing and equipment;

(vi) Instructions for the handling of spills, emergency and cleanup procedures;

(vii) The purpose for and a description of the medical surveillance program required by this standard; and

(viii) An explanation of the importance of engineering and work practice controls for employee protection and any necessary instruction in the use of these controls.

(4) Access to training materials. (i) The employer shall make readily available, without cost, to all affected employees all written materials relating to the employee training program.

(ii) The employer shall provide upon request, all information and training materials relating to the employee information and training program to the Assistant Secretary and the Director.

(o) *Warning Statements.* (1) The employer shall assure that precautionary warnings are affixed to all containers of liquids containing EDB within the workplace.

(2) The employer shall assure that the precautionary warnings are affixed when the materials are sold, distributed, or otherwise leave the employer's workplace.

(3) Substitute Warning Labels. (i) The employer may use warning labels required by other statutes, regulations, or ordinances which impart the same information as the warning statements required by this paragraph.

(A) The employer shall assure that no statement appears on or near any warning information required by this section which contradicts or detracts from the meaning of the required warning.

(B) The employer shall assure that required warning statements are readily visible and legible

(ii) The warning statement shall contain the following information:

DANGER (TRADE NAME) CONTAINS ETHYLENE DIBROMIDE (EDB) CANCER AND REPRODUCTIVE HAZARD, AVOID INHALATION AND SKIN CONTACT

(p) *Recordkeeping.* (1) Exposure monitoring. (i) The employer shall establish an maintain an accurate record of all monitoring required by paragraph (e) of this section.

(ii) This record shall include:

(A) The date(s), number, duration, location and results of each of the samples taken.

(B) The operation involving exposure to EDB which is being monitored;

(C) Name, social security number and job classification of the employee monitored and of all other employees whose exposure the measurement is intended to represent;

(D) Where representative samples are used to document employee exposure, an explanation of why they are characteristic of that employee's exposure.

(E) The type of respiratory protection and other personal protective devices worn, if any; and

(F) A description of the sampling and analytical methods used and evidence of their accuracy.

(2) Medical Surveillance. (i) The employer shall establish and maintain accurate records for each employee subject to medical surveillance required by this standard.

(ii) This record shall include:

(A) The name, social security number and description of the duties of the employee;

(B) A copy of the physician's written opinion;

(C) Results of employee's exposure; and

(D) Any employee medical complaints related to exposure to EDB.

(iii) The employer shall keep the following medical records:

(A) A copy of the medical examination results including the medical and work history required by this section;

(B) A copy of the test results.

(3) Respirator Fit Testing. (i) The employer shall establish and maintain accurate records for each employee subject to negative pressure respirator fit testing required by this standard.

(ii) This record shall include:

(A) A copy of the protocol for either the quantitative or qualitative procedure(s) selected for respirator fit testing.

(B) A copy of the results of any quantitative fit testing performed.

(C) The size and manufacturer types of respirators available for selection.

(D) The type and facepiece selected for the employee.

(E) The date of the most recent fit testing.

(F) The name, social security number, and a description of the duties of tested employee.

(4) Record Retention. The employer shall retain records required by this standard for at least the following periods: (i) Exposure records shall be kept for 30 years.

(ii) Medical records shall be kept for the duration of employment plus 30 years.

(iii) Respirator fit test records shall be kept for 1 year or until replaced with a more recent record.

(iv) Records required by this standard shall be maintained in accordance with 29 CFR 1910.20.

(5) Availability. (i) The employer shall assure that all records to be maintained by this section be made available upon request to the Assistant Secretary and the Director for examination and copying.

(ii) Employee exposure monitoring records required by this paragraph shall be provided upon request for examination and copying to employees, employee representatives, and the Assistant Secretary in accordance with 29 CFR 1910.20 (a)–(e) and (g)–(i).

(iii) Employee medical records required by this pragraph shall be provided upon request for examination and copying, to the subject employee, to anyone having the specific written consent of the subject employee, and to the Assistant Secretary.

(6) Transfer of records. (i) The employer shall comply with the requirements involving transfer of records set forth in 29 CFR 1019.20(h).

(ii) If the employer ceases to do business and there is no successor employer to receive and retain the records for the prescribed period, the employer shall transmit these records by mail to the Director.

(q) *Effective Dates.* (1) Paragraph (a) through (q) of this section shall become effective sixty (60) days following publication of the final rule unless noted below.

(2) Measurements representative of employee esposure to EDB taken in the preceding six months may be used to fulfill the initial monitoring requirement provided the sampling and analytical methods used meet the accuracy and confidence levels required by this paragraph.

(3) Engineering and work practice controls required by paragraph (g) of this section shall be implemented as soon as possible but no later than 2 years after the effective date of the final rule.

(r) *Appendices.* (1) The information and procedures contained in Appendix A is mandatory.

(2) The information contained in the subsequent appendices B, C, and D to this section is not intended by itself, to create any additional obligations not otherwise imposed by this standard nor detract from any existing obligations.

Appendix A—To Section 1910.1043—Qualitative Fit Test Protocols

This appendix specifies the only allowable qualitative fit test protocols permissible for compliance with 29 CFR 1910.1048(h)(4)(ii) and must be used with negative pressure respirators if quantitative fit testing is not used.

I. Isoamyl Acetate Protocol

A. Odor Threshold Screening

1. Three 1-liter glass jars with metal lids (e.g. Mason or Bell jars) are required.

2. Odor-free water (e.g. distilled or spring water) at approximately 25° C shall be used for the solutions.

3. The isoamyl acetate (IAA) (also known as isopentyl acetate) stock solution is prepared by adding 1 cc of pure IAA to 800 cc of odor free water in a 1-liter jar and shaking for 30 seconds. This solution shall be prepared new at least weekly.

4. The screening test shall be conducted in a room separate from the room used for actual fit testing. The two rooms shall be well ventilated but shall not be connected to the same recirculating ventilation system.

5. The odor test solution is prepared in a second jar by placing 0.4 cc of the stock solution into 500 cc of odor free water using a clean dropper or pipette. Shake for 30 seconds and allow to stand for two to three minutes so that the IAA concentration above the liquid may reach equilibrium. This solution may be used for only one day.

6. A test blank is prepared in a third jar by adding 500 cc of odor free water.

7. The odor test and test blank jars shall be labelled 1 and 2 for jar identification. If the labels are put on the lids they can be periodically peeled, dried off and switched to maintain the integrity of the test.

8. The following instructions shall be typed on a card and placed on the table in front of the two test jars (i.e. 1 and 2): "The purpose of this test is to determine if you can smell banana oil at a low concentration. The two bottles in front of you contain water. One of these bottles also contains a small amount of banana oil. Be sure the covers are on tight, then shake each bottle for two seconds. Unscrew the lid of each bottle, one at a time, and sniff at the mouth of the bottle. Indicate to the test conductor which bottle contains banana oil."

9. The mixtures used in the IAA odor detection test shall be prepared in an area separate from where the test is performed, in order to prevent olfactory fatigue in the subject.

10. If the test subject is unable to correctly identify the jar containing the odor test solution, the IAA qualitative fit test may not be used.

1. If the test subject correctly identifies the jar containing the odor test solution, the test subject may proceed to respirator selection and fit testing.

B. Respirator Selection

1. The test subject shall be allowed to pick the most comfortable respirator from a selection including respirators of various

sizes from different manufacturers. The selection shall include at least three sizes of elastomeric half facepieces and units from at least two manufacturers.

2. The selection process shall be conducted in a room separate from the fit-test chamber to prevent odor fatigue. Prior to the selection process, the test subject shall be shown how to put on a respirator, how it should be positioned on the face, how to set strap tension and how to determine a "comfortable" respirator. A mirror shall be available to assist the subject in evaluating the fit and positioning of the respirator. This instruction may not constitute the subjects formal training on respirator use, as it is only a review.

3. The test subject should understand that the employee is being asked to select the respirator which provides the most comfortable fit. Each respirator represents a different size and shape and, if fit properly and used properly will provide adequate protection.

4. The test subject holds each facepiece up to the face and eliminates those which obviously do not give a comfortable fit. Normally, selection will begin with a half-mask and if a good fit cannot be found, the subject will be asked to test the full facepiece respirators. (A small percentage of users will not be able to wear any half-mask.)

5. The more comfortable facepieces are noted; the most comfortable mask is donned and *worn at least five minutes* to assess comfort. Assistance in assessing comfort can be given by discussing the points in #6 below. If the test subject is not familiar with using a particular respirator, the test subject shall be directed to don the mask several times and to adjust the straps each time to become adept at setting proper tension on the straps.

6. Assessment of comfort shall include reviewing the following points with the test subject and allowing the test subject adequate time to determine the comfort of the respirator:

- Positioning of mask on nose.
- Room for eye protection.
- Room to talk.
- Positioning mask on face and cheeks.

7. The following cirteria shall be used to help determine the adequacy of the respirator fit:

- Chin properly placed.
- Strap tension.
- Fit across nose bridge.
- Distance from nose to chin.
- Tendency to slip.
- Self-observation in mirror.

8. The test subject shall conduct the conventional negative and positive-pressure fit checks (e.g. see ANSI Z88.2-1980). Before conducting the negative- or positive-pressure test the subject shall be told to "seat" the mask by rapidly moving the head from side-to-side and up and down, while taking a few deep breaths.

9. The test subject is now ready for fit testing.

10. After passing the fit test, the test subject shall be questioned again regarding the comfort of the respirator. If it has become uncomfortable, another model of respirator shall be tried.

11. The employee shall be given the opportunity to select a different facepiece and be retested if the chosen facepiece becomes increasingly uncomfortable at any time.

C. Fit Test

1. The fit test chamber shall be similar to a clear 55 gal drum liner suspended inverted over a 2 foot diameter frame, so that the top of chamber is about 6 inches above the test subject's head. The inside top center of the chamber shall have a small hook attached.

2. Each respirator used for the fitting and fit testing shall be equipped with organic vapor cartridges or offer protection against organic vapors. The cartridges or masks shall be changed at least weekly.

3. After selecting, donning, and properly adjusting a respirator, the test subject shall wear it to the fit testing room. This room shall be separate from the room used for order threshold screening and respirator selection, and shall be well ventilated, as by an exhaust fan or lab hood, to prevent general room contamination.

4. A copy of the following test exercises and rainbow passage shall be taped to the inside of the test chamber:

Test Exercises

i. Breathe normally.

ii. Breathe deeply. Be certain breaths are *deep* and *regular*.

iii. Turn head all the way from one side to the other. Inhale on each side. Be certain movement is complete. Do not bump the respirator against the shoulders.

iv. Nod head up-and-down. Inhale when head is in the full up position (looking toward ceiling). Be certain motions are complete and made about every second. Do not bump the respirator on the chest.

v. Read the Rainbow passage. Be certain to read aloud and slowly.

vi. Breathe normally.

Rainbow Passage

When the sunlight strikes raindrops in the air, they act like a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond reach, his friends says he is looking for the pot of gold at the end of the rainbow.

5. Each test subject shall wear the respirator for at least 10 minutes before starting the fit test.

6. Upon entering the test chamber, the test subject shall be given a 6 inch by 5 inch piece of paper towel or other porous absorbent single ply material, folded in half and wetted with three-quarters of one cc of pure IAA. The test subject shall hang the wet towel on the hook at the top of the chamber.

7. Allow two minutes for the IAA test concentration to be reached before starting the fit-test exercises. This would be an appropriate time to talk with the test subject, to explain the fit test, the importance of cooperation, the purpose for the head exercises, or to demonstrate some of the exercises.

8. Each exercise described in #4 above shall be performed for at least one minute.

9. If at any time during the test, the subject detects the banana-like odor of IAA, the test has failed, the subject shall quickly exit from the test chamber and leave the test area to avoid olfactory fatigue.

10. If the test is failed, the subject shall return to the selection room and remove the respirator, repeat the odor sensitivity test, select and put on another respirator, return to the test chamber, and again begin the procedure described in the c(4) through c(8) above. The process continues until a respirator that fits well has been found. Should the odor sensitivity test be failed, the subject shall wait about 5 minutes before retesting. Odor sensitivity will usually have returned by this time.

11. If a person cannot pass the fit test described above wearing a half-mask respirator from the available selection, full facepiece models must be used.

12. When a respirator is found that passes the test, the subject breaks the faceseal and takes a breath before exiting the chamber. This is to assure that the reason the test subject is not smelling the IAA is the good fit of the respirator facepiece seal and not olfactory fatigue.

13. When the test subject leaves the chamber, the subject shall remove the saturated towel and return it to the person conducting the test. To keep the area from becoming contaminated, the used towels shall be kept in a self-sealing bag so there is no significant IAA concentration buildup in the test chamber during subsequent tests.

14. Persons who have successfully passed this fit test with a half-mask respirator may be assigned the use of the test respirator in atmospheres with up to 10 times the PEL of airborne EDB. In atmospheres greater than 10 times, and less than 100 times the PEL (up to 10 ppm), the subject must pass the IAA test using a full face negative pressure respirator.

II. Saccharin Solution Aerosol Protocol

A. Respirator Selection

Respirators shall be selected as described in section IB (respirator selection) above, except that each respirator shall be equipped with a particulate filter cartridge.

B. Taste Threshold Screening

An enclosure about head and shoulders shall be used for threshold screening (to determine if the individual can taste saccharin) and for fit testing. The enclosure shall be approximately 12 inches in diameter by 14 inches tall with at least the front clear to allow free movement of the head when a respirator is worn.

2. The test enclosure shall have a three-quarter inch hole in front of the test subject's nose and mouth area to accommodate the nebulizer nozzle.

3. The entire screening and testing procedure shall be explained to the test subject prior to conducting the screening test.

4. During the threshold screening test, the test subject shall don the test enclosure and

breathe with open mouth with tongue extended.

5. Using a DeVilbiss Model 40 Inhalation Medication Nebulizer or equivalent, the test Conductor shall spray the threshold check solution into the enclosure. This nebulizer shall be clearly marked to distinguish it from the fit test solution nebulizer.

6. The threshold check solution consists of 0.83 grams of sodium saccharin, USP in water. It can be prepared by putting 1 cc of the test solution (see C8 below) in 100 cc of water.

7. To produce the aerosol, the nebulizer bulb is firmly squeezed so that it collapses completely, then is released and allowed to fully expand.

8. Ten squeezes of the nebulizer bulb are repeated rapidly and then the test subject is asked whether the saccharin can be tasted.

9. If the first response is negative, ten more squeezes of the nebulizer bulb are repeated rapidly and the test subject is again asked whether the saccharin can be tasted.

10. If the second response is negative ten more squeezes are repeated rapidly and the test subject is again asked whether the saccharin can be tasted.

11. The test conductor will take note of the number of squeezes required to elicit a taste response.

12. If the saccharin is not tasted after 30 squeezes (Step 10), the saccharin fit test cannot be performed on the test subject.

13. If a taste response is elicited, the test subject shall be asked to take note of the taste for reference in the fit test.

14. Correct use of the nebulizer means that approximately 1 cc of liquid is used at a time in the nebulizer body.

15. The nebulizer shall be thoroughly rinsed in water, shaken dry, and refilled at least every four hours. *C. Fit Test*

1. The fit test uses the same enclosure described in IIB above.

2. Each test subject shall wear the respirator for a least 10 minutes before starting the fit test.

3. The test subject shall don the enclosure while wearing the respirator selected in section IB above. This respirator shall be properly adjusted and equipped with a particulate filter cartridge.

4. The test subject may not eat, drink (except plain water), or chew gum for 15 minutes before the test.

5. A second DeVilbiss Model 40 Inhalation Medication Nebulizer is used to spray the fit test solution into the enclosure. This nebulizer shall be clearly marked to distinguish it from the screening test solution nebulizer.

6. The fit test solution is prepared by adding 83 grams of sodium saccharin to 100 cc of warm water.

7. As before, the test subject shall breathe with mouth open and tongue extended.

8. The nebulizer is inserted into the hole in the front of the enclosure and the fit test solution is sprayed into the enclosure using the same technique as for the taste threshold screening and the same number of squeezes required to elicit a taste response in the screening. (See B8 through B10 above).

9. After generation of the aerosol read the following instructions to the test subject. The test subject shall perform the exercises for one minute each.

i. Breathe normally.

ii. Breathe deeply. Be certain breaths are *deep* and *regular*.

iii. Turn head all the way from one side to the other. Be certain movement is complete. Inhale on each side. Do not bump the respirator against the shoulders.

iv. Nod head up-and-down. Be certain motions are complete. Inhale when head is in the full up position (when looking toward the ceiling). Do not to bump the repirator on the chest.

v. Read the Rainbow Passage. Be certain to read aloud and slowly.

vi. Breathe normally.

10. The Rainbow Passage as given below shall be printed on a card so the test subject may read it.

Rainbow Passage

When the sunlight strikes raindrops in the air, they act like a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow.

11. At the beginning of each exercise, the aerosol concentration shall be replenished using one-half the number of squeezes as initially described in C8.

12. The test subject shall indicate to the test conductor if at any time during the fit test the taste of saccharin is detected.

13. If the saccharin is detected the fit is deemed unsatisfactory and a different respirator shall be tried.

14. Successful completion of the test protocol shall allow the use of the tested respirator in contaminated atmospheres up to 10 times the PEL. In other words this protocol may be used assign protection factors no higher than ten.

III. Irritant Fume Protocol

A. Respirators Shall Be Selected as Described in Section IB Above, Except That Each Respirator Shall be Equipped With High-Efficiency Acid-Gas Organic Vapor Cartridges

B. Fit Test

1. The test subject shall be allowed to smell a weak concentration of the irritant smoke to familiarize the subject with the characteristic odor.

2. The test subject shall properly don the respirator selected as above, and wear it for at least 10 minutes before starting the fit test.

3. The test conductor shall review this protocol with the test subject before testing.

4. The test subject shall perform the conventional positive pressure and negative pressure fit checks (see ANSI Z88.2 1980). Failure of either check shall be cause to select an alternate respirator.

5. Break both ends of a ventilation smoke tube containing stannic oxychloride, such as the MSA part #5645, or equivalent. Attach a short length of tubing to one end of the smoke tube. Attach the other end of the smoke tube to a low pressure air pump set to deliver 200 milliliters per minute.

6. Advise the test subject that the smoke can be irritating to the eyes and instruct the subject to keep the eyes closed while the test is performed.

7. The test conductor shall direct the stream of irritant smoke from the tube towards the faceseal area of the test subject. The person conducting the test shall begin with the tube at least 12 inches from the facepiece and gradually move to within one inch, moving around the whole perimeter of the mask.

8. The test subject shall be instructed to do the following exercises while the respirator is being challenged by the smoke. Each exercise shall be performed for one minute.

i. Breathe normally.

ii. Breathe deeply. Be certain breaths are *deep* and *regular*.

iii. Turn head all the way from one side to the other. Be certain movement is complete. Inhale on each side. Do not bump the respirator against the shoulders.

iv. Nod head up-and-down. Be certain motions are complete and made every second. Inhale when head is in the full up position (looking toward ceiling). Do not bump the respirator against the chest.

v. Slowly and distinctly, count backwards from 100.

vi. Breathe normally.

9. The test subject shall indicate to the test conductor if the irritant smoke is detected. If smoke is detected, the test conductor shall stop the test. In this case, the tested respirator is rejected and another respirator shall be selected.

10. Each test subject passing the smoke test (i.e. without detecting the smoke) shall be given a sensitivity check of smoke from the same tube to determine if the test subject reacts to the smoke. Failure to evoke a response shall void the fit test.

11. Steps B4, B9, B10 of the fit test protocol shall be performed in a location with exhaust ventilation sufficient to prevent general contamination of the testing area by the test agents.

12. Respirators succesfully tested by the protocol may be used in contaminated atmospheres up to ten times the PEL.

Appendix B—To Section 1013.1048—Technical Data for Ethylene Dibromide

I. Physical and Chemical Data

A. Substance Identification

1. Synonyms: Aadibroom, bromofume, celmide, dibromethane, 1,2-dibromoethane, sym-dibromoethane, Dowfume EDB, Dowfume MC-2, Dowfume W-8, Dowfume W-85, Dowfume 40, E-D-BEE, EDB, EDB-85, ENT 15,349, ethylene dibromide, Fume-Gas, glycol dibromide, Isobromo D, Kopfume, Nefis, Pestmaster, Pestmaster EDB—85, Sanhyuum, Soilbrum-40, Soilbrum-85, Soilfume, Unifume.

2. Formula: Ch_2BrCH_2Br.

3. Molecular Weight: 187.9.

B. Physical Data

1. Boiling Point (760 mm Hg): 131° C (268° F).
2. Melting Point 9.6° C. (47.2° F).
3. Specific Gravity (Water=1) 2.18.
4. Vapor Density (Air=1 at boiling point of EDB): 6.5.
5. Vapor pressure at 20° C (68° F): 11 mm Hg.
6. Solubility in water, % by weight at 20° C (68° F): 0.4.
7. Appearance and odor: Colorless liquid or solid with a mild, sweet odor at high concentrations.
8. Odor Threshold: 10 parts per million.

II. Fire, Explosion, and Reactivity Hazard Data

A. Fire: Not Combustible

B. Reactivity

1. Conditions contributing to instability: High temperature; ethylene dibromide slowly decomposes in the presence of light.
2. Hazardous decomposition products: Toxic gases and vapors (such as hydrogen bromide, bromine, and carbon monoxide) may be released when ethylene dibromide decomposes.
3. Incompatibilities: Reacts with chemically active metals, such as sodium, potassium, calcium, powdered aluminum, magnesium and zinc; strong alkalies, and oxidizing agents; Reacts with certain metals, such as aluminum and magnesium to form combustible and explosive organometallic compounds and liquid ammonia.
4. Special precautions: Liquid ethylene dibromide will attack some forms of plastic, rubber, and coatings.

III. Spill, Leak, and Disposal Procedures

A. If ethylene dibromide leaks or is spilled, the following steps should be taken:

(1) Evacuate all non-essential personnel from the area.

(2) Ventilate the area of the spill or leak to prevent accumulation of the vapor.

(3) If in liquid form, collect spilled material for reclamation or absorb in vermiculite, dry sand, earth, or similar nonreactive material.

B. Personnel entering the spill or leak area shall be furnished the appropriate personal protective equipment. All other people shall be excluded from the area.

C. EDB contaminated waste, debris, containers, or equipment shall be disposed of in sealed, labeled containers which prevent dispersion of EDB outside the container.

IV. Health Hazard Data

A. Route of Entry

Inhalation is the most common source of occupational exposure to ethylene dibromide. EDB may also be absorbed through the skin after direct contact with either the liquid or vapor. It is also readily absorbed from the gastrointestinal tract after being ingested. It is, therefore important to maintain good personal hygiene and housekeeping practices when working with EDB.

B. Adverse Health Effects

1. Acute Effects

Immediate.—EDB is an irritant to the eyes, respiratory tract and mucous membranes; inhalation exposure in humans has been associated with headache, decreased appetite, inability to sleep, nausea, and dizziness. Dermal contact may result in intense burning pain, swelling and blistering. Repeated contact may cause skin sensitization.

Delayed.—Although the acute symptoms may subside, loss of consciousness and death due to liver and kidney failure have occurred twelve to seventy-two hours after an acute exposure to EDB. Therefore, it is very important to immediately report all acute exposures to EDB.

2. Chronic Effects

EDB has the potential for causing cancer and adverse reproductive effects in humans. These effects have been demonstrated in various animal experiments which show EDB to be a potent cancer agent and reproductive toxin.

V. Monitoring and Measurement Procedures

A. Eight-hour exposure evaluation: The average 8-hour employee exposure may be determined from two (2) 4-hour samples. Air samples should be taken in the employee's breathing zone.

B. Short Term Exposure Limit (STEL) Evaluation: Measurements taken for the purpose of determining employee exposure under this section must be taken during periods of maximum expected airborne concentrations of EDB in the employee's breathing zone. The sampling time for STEL evaluation is fifteen (15) minutes.

C. Monitoring techniques: The employer shall use a method of exposure measurement which has an accuracy (with a confidence level of 95%) of not less than plus or minus 25 percent for concentrations of EDB at the action level of 0.05 ppm.

D. Sampling and analysis under this section may be performed by collecting EDB on charcoal absorption tubes with subsequent chemical analysis by gas chromatograph. This Appendix D contains a method for EDB analysis which has been tested by OSHA at concentrations below 0.1 ppm.

VI. Medical Surveillance

A. Periodic

A medical surveillance program shall be provided by the employer at no expense to all employees who are exposed to EDB at or above the action level for 30 or more days per year or those employees required to wear a respirator regardless of the duration of exposure. The program shall be administered at the time of initial assignment and annually thereafter.

It shall consist of:

(a) A detailed work and medical history.

(b) A complete physical examination.

(c) Pertinent laboratory examination to ascertain liver, kidney and other abnormalities associated with EDB exposure.

In addition for those employees required to wear a respirator, the medical surveillance program shall include an assessment of pulmonary status which will include a chest X-ray initially and every 5 years (unless indicated more frequently by the examining physician) and a pulmonary function test.

Medical surveillance can play a very important role in protecting employee's health. All employees are encouraged strongly to participate. The employer shall provide the following information to the physician:

(1) a description of the employee's duties as they relate to ethylene dibromide exposure;

(2) the exposure level;

(3) a description of the personal protective equipment the employee is required to wear; and

(4) the results of prior medical examinations and opinions concerning the employee's health.

After a medical examination the physician must prepare a written report containing:

(1) the physician's opinion as to whether the employee has any medical condition which places that employee at an increased risk of material impairment to health from exposure to ethylene dibromide;

(2) any recommended special protective measures to be provided; and

(3) any recommended limitation on the use of respirators.

B. Additional

Medical consultation must be made available as soon as possible if the employee is experiencing signs or symptoms of EDB poisoning.

C. Emergency

In the event that an employee is exposed to EDB in an emergency situation or develops signs or symptoms associated with acute toxicity from EDB exposure, the employer shall immediately provide the employee with a medical examination. This examination shall include all the steps necessary to stabilize the health of the employee and a 72 hour medical observation period to assure that the often unexpected, serious, delayed systemic effects from acute exposure are minimized.

Appendix C—To Section 1019.1045—Medical Surveillance Guidelines for Ethylene Dibromide

I. Introduction

The primary purpose of the Occupational Safety and Health Act of 1970 is to assure, so far as possible, safe and healthful working conditions for every man and woman. The occupational health standard for ethylene dibromide (EDB) was promulgated to protect workers involved in the production, reaction, release, mixing, blending, packaging, repackaging, storage, transportation, handling, distribution, and use of EDB and products containing EDB. Under the final standard occupational exposure to EDB is to be limited to 0.1 ppm based on 8-hour time weighted average (TWA) with a STEL of 0.5 ppm. Employee exposure must be controlled to or below these levels through a combination of engineering, work practices, and other administrative controls.

The standard also provides for a medical surveillance program for all employees required to wear a respirator or employees exposed to levels of EDB at or above the action level of 0.05 ppm averaged over an 8-

hour period (TWA) for 30 or more days per year. The purpose of this document is to outline the medical surveillance provisions of the standard for EDB, and to provide further information to the physician regarding the examination and evaluation of workers exposed to EDB.

Section II provides a description of the medical surveillance program, notification and recordkeeping requirements for the employer and a discussion of the requirements for respirator use.

Section III discusses the acute and chronic effects associated with EDB exposure in man and experimental animal models. Included in this discussion are the carcinogenic, reproductive, and mutagenic effects seen in animal experiments and epidemiological studies.

Section IV outlines the recommended medical evaluation for workers exposed to EDB including details of the work and medical history, physical examination, recommended laboratory tests and medical procedures for emergency situations.

II. Medical Surveillance

Under the occupational health standard for EDB, the employer must make available a medical surveillance program for any employee required to wear a respirator or any employee exposed to EDB at or above the action level for a total of 30 or more days per year.

The medical surveillance program will include a medical and occupational history, including a reproductive history, a comprehensive medical examination and laboratory evaluation (if indicated). Employees who are required to wear a respirator must have an assessment of pulmonary status in addition to the other medical surveillance requirements.

The frequency of these examinations will be at the time of initial assignment and annually thereafter. The employer must provide the examining physician with following specific information: a copy of the EDB standard and appendices B and C, a description of the employee's duties as related to exposure, the exposure level to EDB, a description of personal protective equipment used, and all prior written medical opinions, regarding the employee, in the employer's possession or control.

For each examination required under this section, the employer shall obtain a written opinion from the examining physician which shall include:

(1) The physician's opinion as to whether the employee has any detected medical conditions or is taking any medications which would place the employee at increased risk of material impairment from exposure to EDB.

(2) Any recommended limitations on the employee's exposure to EDB or upon the use of personal protective equipment; this will include an opinion as to the employee's ability to wear a respirator.

(3) A statement that the employer has been informed by the physician of the results of the medical examinations and any medical conditions resulting from EDB exposure which require further explanation or treatment.

As part of the medical surveillance program, the physician must assess the pulmonary status of each employee who will be wearing a respirator. This assessment will include a chest x-ray initially and additional x-rays at least every five years or more frequently if indicated by the examining physician, and an annual pulmonary function test (detailed in Section IV).

The employer shall instruct the physician not to reveal in the written opinion given to the employer specific findings or diagnosis unrelated to occupational exposure. The employer shall provide a copy of the physician's written opinion to the affected employee within 15 days from its receipt.

III. Toxicology of Ethylene Dibromide

Both acute and chronic health effects associated with EDB exposure must be considered. The acute health effects seen in man include both immediate and delayed responses which are well documented. However, chronic toxicity in humans such as carcinogenicity, mutagenicity and adverse reproductive effects have to be derived from animal models.

Acute Effects

Immediate

Ethylene dibromide (EDB) is rapidly absorbed from the lungs when breathed as a vapor, from the gastrointestinal tract when taken by mouth, and through the skin on direct contact with the liquid form.

EDB is an irritant to the eyes, respiratory tract and mucous membranes. Inhalation exposure in humans has been associated with headache, decreased appetite, inability to sleep, nausea, and dizziness. Dermal contact may result in intense burning pain, swelling, blistering, and repeated contact may cause skin sensitization. Deaths have occurred following the inadvertent ingestion and inhalation of EDB. In one reported incident, accidental ingestion of 4.5 ml of EDB produced vomiting, diarrhea, abdominal pain, renal failure and death within 54 hours with central lobular necrosis of the liver and focal proximal tubular epithelial damage in the kidney found on autopsy.

Delayed.

Recently, while cleaning a storage tank, two workers at a California pesticide storage and formulation facility were exposed to an air concentration of EDB in excess of 28 ppm and had skin contact with a .3% solution of EDB. Both workers experienced intermittent loss of consciousness, agitation, nausea, and diarrhea, all of which appeared to be transient symptoms. However, at 12 and 72 hours respectively, post exposure, both workers died. Autopsies revealed dermal burns, extensive heart, kidney, liver and lung damage. It is important to note here the time sequence between exposure, symptoms and death.

Chronic Effects

Chronic health effects in humans and animals associated with EDB exposure can be divided into carcinogenic, reproductive and mutagenic effects.

Carcinogenic

EDB has been shown to cause cancer orally or by inhalation in 3 strains of rats and 2 strains of mice. In rats and mice, cancer was produced by inhalation exposures as low as 10 ppm. These animal data indicate that EDB is a *potential human carcinogen.* An epidemiologic study of cancer mortality provides suggestive evidence of excess cancer risk in workers exposed to EDB, but because of methodological weaknesses, this study is inconclusive. Studies in animals dosed with disulfiram and EDB clearly indicate a synergistic carcinogenic effect. Therefore, workers taking disulfiram (Antabuse®) may be at increased risk of these health effects because the two pathways involved in EDB metabolism are altered by this drug.

Reproductive/Mutagenic

EDB has been shown to be a mutagen and teratogen as well as a testicular toxin in several species of animals at levels of inhalation exposure as low as 10 ppm. Available human epidemiological data provide inconclusive evidence that EDB may affect fertility in male workers exposed to EDB due to methodological problems with the studies. The animal data noted above implies that EDB may potentially affect human reproductive capacity and the offspring of male or female EDB workers.

IV. Medical Evaluation

As discussed in Section III, EDB is a potential human carcinogen causing a variety of neoplasms including stomach, nasal, and lung cancers in experimental animals and a potential human reproductive hazard causing pathological changes in sperm, testes and fertility status in experimental animals. EDB is also a known human liver, kidney, skin and central nervous system toxin. It is therefore extremely important for the examining physician to evaluate the EDB-exposed worker carefully and completely and to focus the examination on these potential health hazards.

The medical evaluation should include a detailed work and medical history, a pertinent review of systems, a complete physical examination and laboratory studies to monitor potential biological changes.

A complete and detailed work history is important in the initial evaluation. A listing of all previous employment with information on work processes, exposure to EDB or other toxic substances, respiratory protective equipment used, and previous medical surveillance should all be included in the worker's record. Information concerning on-the-job personal hygiene, smoking or eating habits in work areas, laundry procedures, and use of any protective clothing or respiratory protective equipment should be noted.

The medical history should include a listing of all past and current medical conditions, especially any neurological, gastrointestinal, kidney, dermatological, genetic or reproductive problems. Also, a list of current medication especially disulfiram (Antabuse®), previous surgeries, hospitalizations, allergies,

smoking history and alcohol consumption should be noted.

A complete review of systems should be performed to assess both recognized complaints and subtle or slowly acquired symptoms which the worker might not appreciate as being significant. The review of symptoms should include the following:

General—weight loss, fatigue, malaise.

Head, eyes, ears, nose, throat—headache, dizziness, and visual disturbances, nasal irritation.

Cardio-pulmonary—shortness of breath, cough, tachypnea, tachycardia and chest pain.

Gastrointestinal—nausea, vomiting, decreased appetite, abdominal pain, jaundice, diarrhea.

Genito-urinary—history of infertility, impotence, loss of libido, abnormal menstrual periods, history of miscarriages, still births, kidney failure, oliguria, and testicular disease.

Skin—rashes, vesicles, and burns.

Neurological—insomnia, fatigue, dizziness, confusion, and depression.

The physical examination should emphasize the pulmonary, cardiac, neurological, gastrointestinal, genito-urinary, and dermal systems. Included in this examination should be a complete assessment of the employee's ability to wear a respirator (if required). This should include a complete head, eyes, ears, nose, throat, thorax and pulmonary examination.

A complete neurological examination should include an adequate mental status evaluation including a search for behavioral and psychological disturbances, memory testing, evaluation for irritability, insomnia, hallucination, depression, restlessness and nervousness.

The abdominal examination should include auscultation for bowel sounds and abdominal bruits and palpation for hepatomegaly, masses, and diffuse abdominal tenderness.

Genito-urinary examination should include examination of testicles in male employees and pelvic examination in female employees.

The dermal examination should focus on evidence of jaundice, burns or blistering.

As part of the medical evaluations, the standard requires that the following laboratory studies be performed:

(1) Serum calcium, phosphorus, glucose, blood urea nitrogen, urea acid, creatinine, cholesterol, total protein, albumin, alkaline phosphatase, LDH, SGOT, SGPT and GGTP.

(2) Routine urinalysis with microscopic examination.

Further, the phyician is authorized to recommend any additional laboratory or other test which is deemed necessary in accordance with sound medical practice.

In addition, the standard requires that the following examinations be performed if the employee is going to wear a respirator:

(3) Chest X-ray (posterior-anterior and lateral views) to be performed initially and at 5 year intervals (unless indicated more frequently by the examining physician).

(4) Pulmonary function testing; including FVC and FEV_1 with interpretation.

This test allows those individuals who will be exposed above the PEL regardless of the duration of exposure to be included in the medical surveillance program.

In addition, respirator usage presents an excess burden to the pulmonary system of the employee. This burden may result in symptoms such as shortness of breath, chest pain, dizziness or fatigue. All of these symptoms will be greatly exacerbated by pre-existing lung disease such as chronic bronchitis, emphysema, asthma or pneumoconiosis. It is, therefore, imperative that all employees who will be wearing respirators be medically screened to determine fitness for respirator usage. OSHA believes that the physician can best accomplish this through utilization of a physical examination, including a pulmonary function test and a chest x-ray.

Emergency Situations

In the event that an employee is exposed to EDB in an emergency situation or develops signs or symptoms associated with acute toxicity from EDB exposure, the employer shall immediately provide the employee with a medical examination. This examination shall include all the steps necessary to stabilize the health of the employee and a 72 hour medical observation period to assure that the often unexpected, serious delayed systemic effects from acute exposure are minimized. This observation period should take place in a medical facility, preferably a hospital, where a licensed physician will be responsible for supervising all medical care delivery.

Appendix D—To Section 1013.1048—OSHA Laboratory Modification of NIOSH Method P&CAM 260

Analyte: Ethylene dibromide
Matrix: Air
Procedure: Adsorption on charcoal, desorption with 10% CS_2 in benzene, GC

1. Principle of method.
   1.1 A known volume of air is drawn through a charcoal tube to trap the organic vapors present.
   1.2 The charcoal in the tube is transferred to a small, stoppered sample vial, and the analyte is desorbed with 10% CS_2 in benzene.
   1.3 An aliquot of the desorbed sample is injected into a gas chromatograph.
   1.4 The area of the resulting peak is determined and compared with areas obtained for standards.
2. Advantages and disadvantages of the method.
   2.1 The sample device is small, portable, and involves no liquids. Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick, instrumental method.
   2.2 The amount of sample which can be taken is limited by the number of milligrams that the tube will hold before overloading. When the sample value obtained for the backup section of the charcoal tube exceeds 25 percent of that found on the front section, the possibility of sample loss exists.
   2.3 The precision of the method is limited by the reproducibility of the pressure drop across the tubes. This drop will affect the flow rate and cause the volume to be imprecise, because the pump is usually calibrated for one tube only.
3. Apparatus.
   3.1 A calibrated personal sampling pump whose flow can be determined within ±5 percent at the recommended flow rate.
   3.2 Charcoal tubes: Glass tube with both ends flame sealed, 7 cm long with a 6-mm O.D. and a 4-mm I.D., containing 2 sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600°C prior to packing. The adsorbing section contains 100 mg of charcoal, the back-up section 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the back-up section. A plug of silicated glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than one inch of mercury at a flow rate of 1 liter per minute.
   3.3 Gas chromatograph equipped with an electron capture detector.
   3.4 Column (10-ft × ⅛-in stainless steel) packed with 100/120 Supelcoport coated with 10 percent SP 1000.
   3.5 An electronic integrator of some other suitable method for measuring peak area.
   3.6 Two-milliliter sample vials with Teflon-lined caps.
   3.7 Microliter syringes: 10-microliter, and other convenient sizes for making standards.
   3.8 Pipets: 1.0-ml delivery pipets.
   3.9 Volumetric flasks: convenient sizes for making standard solutions.
4. Reagents.
   4.1 Chromatographic quality CS_2 and benzene.
   4.2 Ethylene dibromide, reagent grade.
   4.3 Filtered compressed air.
   4.4 Purified nitrogen.
5. Procedure.
   5.1 Cleaning of equipment. All glassware used for the laboratory analysis should be properly cleaned and free of organics which could interfere in the analysis.
   5.2 Calibration of personal pumps. Each pump must be calibrated with a representative charcoal tube in the line.
   5.3 Collection and shipping of samples.
   5.3.1 Immediately before sampling, break the ends of the tube to provide an opening at least one-half the internal diameter of the tube (2 mm).
   5.3.2 The smaller section of the charcoal is used as the backup and should be placed nearest the sampling pump.
   5.3.3 The charcoal should be placed in a vertical position during sampling to minimize channeling through the charcoal.
   5.3.4 Air being sampled should not be passed through any hose or tubing before entering the charcoal tube. EDB is readily absorbed by tygon tubing. This will make the sample results read low. The use of stainless steel tubing will avoid this problem.
   5.3.5 A sample size of 10 liter is recommended. Sample at a flow rate of approximately 0.2 liters per minute. The

flow rate should be known with an accuracy of at least ±5 percent.

5.3.6 The temperature and pressure of the atmosphere being sampled should be recorded.

5.3.7 The charcoal tubes should be capped with the supplied plactic caps immediately after sampling. Rubber caps should not be used.

5.3.8 Submit at least one blank tube (a charcoal tube subjected to the same handling procedures, without having any air drawn through it) with each set of samples.

5.3.9 Take necessary shipping and packing precautions to minimize breakage of samples.

5.4 Analysis of samples.

5.4.1 Preparation of samples. In preparation for analysis, each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a 2-mL vial. The separating section of foam is removed and discarded; the section is transferred to another capped vial. These two sections are analyzed separately.

5.4.2 Desorption of samples. Prior to analysis, 1.0 mL of 10% CS_2 in benzene is pipetted into each sample container. Desorption should be done for 30 minutes with occasional shaking. The sample vials are recapped as soon as the solvent is added.

5.4.3 GC conditions. The typical operating conditions for the gas chromatograph are:

1. 30 mL/min (60 psig) nitrogen carrier gas flow.
2. 250°C Injector temperature.
3. 300° C Detector temperature.
4. 180° C Column temperature.

5.4.4 Injection. Solvent flush technique or equivalent.

5.4.5 Measurement of area. The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below.

5.5 Determination of desorption efficiency.

5.5.1 Importance of determination. The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine, at least once, the percentage of the specific compound that is removed in the desorption process, provided the same batch of charcoal is used.

5.5.2 Procedure for determining desorption efficiency. The reference portion of the charcoal tube is removed. To the remaining portion, amounts representing 0.5X, 1X, and 2X (X represents PEL) based on a 10 L air sample are injected onto several tubes at each level. Dilution of ethylene dibromide with benzene are made to allow injection of measurable quantities. These tubes are then allowed to equilibrate at least overnight. Following equilibration they are analyzed following the same procedure as the samples. The desorption efficiency, amount recovered/amount added, is plotted versus the amount of analyte found. This curve is used to correct for adsorption losses.

6. Calibration and standards.

A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same GC conditions and during the same time period as the unknown samples. Curves are prepared by plotting concentration versus peak area.

Note.—Since no internal standard is used in the method, standard solutions must be analyzed at the same time that the sample analysis is done. This will minimize the effect of known day-to-day variations and variations during the same day of the electron capture detector response. Multiple injections are necessary.

7. Calculations.

Read the weight, corresponding to each peak area from the standard curve, correct for the blank, correct for the desorption efficiency, and make necessary air volume corrections.

[FR Doc. 83-27291 Filed 10-3-83; 4:08 pm]
BILLING CODE 4510-26-M

APPENDIX B

EPIDEMIOLOGIC EVIDENCE ON CANCER RISK AND ETHYLENE DIBROMIDE (EDB) EXPOSURE

Several animal studies have suggested a strong link between exposure to ethylene dibromide (EDB) and increased cancer risk (Olson et al., 1973, NCI, 1978; NTP, 1980; Wong et al., 1982). A bioassay in which both rats and mice were exposed to EDB via inhalation indicated an association with increased incidences of tumors in a wide range of sites, including the nasal cavity, circulatory system, pituitary, and lung (NTP, 1982). Female mice exhibited higher rates of fibrosarcomas of the subcutaneous tissue and adenocarcinomas of the mammary gland, while male rats developed mesotheliomas of the tunica vaginalis. In a study conducted by Midwest Research Institute, (Wong et al., 1982) rats receiving 20 ppm of EDB via inhalation showed excess tumors of the spleen, liver, kidney, mammary gland, and subcutaneous tissue. The wide range of sites at which carcinogenesis was induced by inhalation of EDB is similar to the gavage experiments in which tumors of the forestomach predominated, but again in which a wide range of systemic tumors was induced (NCI, 1978, Olson et al., 1973).

In the light of the experimental evidence, three mortality studies of workers occupationally exposed to EDB have been conducted (one published, two unpublished). Ott et al. (1980) examined mortality of employees who worked in two EDB manufacturing plants in Texas and in Michigan to assess whether excess mortality due to malignancy or respiratory disease was associated with EDB exposure. Turner did two surveys of the mortality experience of employees of EDB manufacturing plants in Wales and England in 1976 and 1977.

I. OCCUPATIONAL EXPOSURES IN THE U.S.

A total of 161 employees constituted the study population at the two U.S. sites. Table 1 compares the two plants. The main differences are 1) that the Texas plant did not manufacture any other organic bromide products while the Michigan plant did, and 2) quantitative data on EDB exposure was only available for the Michigan plant.

Ott et al., conducted a standardized mortality ratio (SMR) analysis of the employees at both sites. No control group of workers unexposed to EDB was studied. Instead, the investigators retrospectively looked at the number of years in each age category contributed by each exposed employee and calculated the expected numbers of deaths based on death statistics for U.S. white males of the same ages. This process of standardizing was done for each five-year period beginning in 1940, and the expected values were summed. Finally, expected numbers of deaths overall, and of neoplasm deaths, were compared with the observed numbers. The differences were found to be not statistically significant, though in one plant the difference for cancer deaths was of borderline significance.

The following sections discuss the aspects of selection, mortality ascertainment, exposure assessment, and statistical analysis.

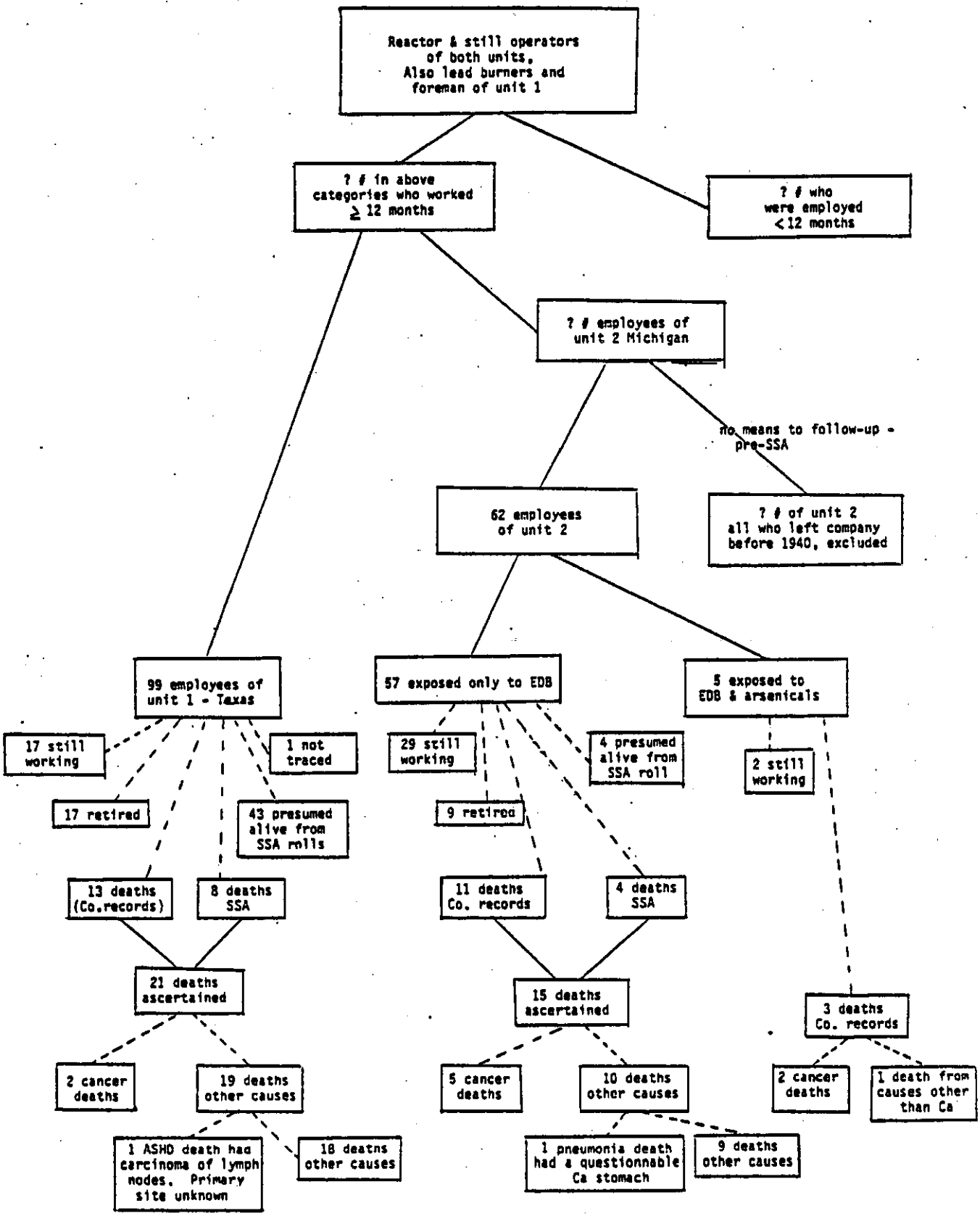
SELECTION

The upper half of Figure 1 shows the selection process of workers whose mortality was studied. The magnitude of loss from those whose employment was less than 12 months is unknown. In the final cohort, 20% of the workers had less than one year exposure, and almost 75% had less than five years, indicating a high turnover in the exposed job categories. It is possible that reactor operators with greater seniority had lower levels of exposure. Enterline and Marsh (1982) found that copper smelter workers in high exposure jobs tended to terminate their employment more quickly than those in low-exposure categories. In such a case, duration of exposure is not an ideal measure of exposure level. Thus any association between "level" of exposure and risk would be underestimated.

A second loss was the group who left the company before 1940. Since these employees were more likely to be older and therefore to have died, some loss of statistical power may have resulted from their exclusion. However, there is no feasible means of thorough follow-up. The method of follow-up used was the Social Security Administration (SSA) records, but this could not be totally accurate because the SSA was established in 1937. The change from batch reactors to continuous reactors in the early 1960s was said to have reduced exposure concentrations. Among those employed since 1940, some may have been exposed only or primarily to the lower levels, while for those employed previously, higher exposure levels may have prevailed. The observed risk levels may therefore underestimate risk among those employed in earlier years.

FIGURE 1

Worker Deaths in Two U.S. EDB Plants



Texas plant = Unit 1
Michigan plant = Unit 2

ASCERTAINMENT

A further source of potential bias is due to the method of ascertaining deaths among those for whom the company had no record. As seen in Figure 1, for the Michigan plant, the SSA identified four deaths and four persons who were still on the SSA rolls and presumed alive. For the Texas plant, the SSA identified eight deaths, 43 person still on the rolls, and one person not traced. This method provides a minimum number of deaths, but the actual number may be higher. Thus, firm data exist for a higher proportion of the Michigan cohort than of the Texas group (53/57 vs. 55/99).

Another source of uncertainty stems from the truncated nature of the data. Since some employees may yet die of cancer, additional years of follow-up may increase the observed cancer deaths. This is not in itself a bias, since the calculation for expected number of cancer deaths is based on years at risk, not future years at risk, and in future years, both expected and observed deaths will increase. However, among the Michigan employees, 21 had less than 15 years since their first exposure, an insufficient period of time for any carcinogenic effect to be expressed. Interestingly, this plant is the one which shows the larger mortality ratio of observed to expected.

EXPOSURE

As can be seen in Table 1, one of the prominent differences between the two plants is the much wider range of chemical exposures at the Michigan plant. Among these chemicals are two which are known to induce cancer and for which there is evidence of carcinogenicity in humans as evaluated by the International Agency for Research on Cancer 1979): benzene (IARC, 1982) and carbon tetrachloride (IARC, 1979). No measurements were reported (it is not clear if any were taken) for these exposures, leaving open the possibility that any observed excess of cancers at the Michigan plant may be due to exposures other than EDB. On the other hand, such an excess could be due to EDB acting synergistically with other carcinogens to elevate risk.

Reactor and distillation operations were conducted at both sites. As indicated above, no measurements relating to EDB were made at the Texas plant where EDB was the only bromide product to which workers were potentially exposed. In the analyses (by Ott et al., 1980 and by Ramsey et al., 1978), the exposures were assumed to be the same at both plants. It is difficult to assess the validity of this assumption, and calculations on the Michigan cohort alone are in order.

At the Michigan plant, work area samples of EDB were taken in 1949, 1952, and 1971-72, but the actual cumulative exposures to the workers are unknown. If exposure levels were considerably lower for some of these workers (and/or for workers at the Texas plant), misclassification would result in a bias underestimating the risk. In

other words, the observed deaths would represent the mortality experience of both exposed workers and those only minimally exposed.

Industrial hygiene measurements of the breathing zone at the Michigan plant taken in 1949 showed a range of 1-7.4 ppm for reactor operators and 2.2-10.6 ppm for still operators. A much wider range of measurements was taken in subsequent years, though only one other measurement was specified to be of the breathing zone, with a range of 1.8-96 ppm for reactor operators in 1975. One question raised by these measurements is whether a discrepancy exists between the claim of reduced exposure since the reactor process change in the 1960s and the seemingly wider range of industrial hygiene samples in more recent years.

Another issue arises in the 1975 sampling where there appears to be a five-fold reduction in going from breathing zone to personnel monitoring. If the personnel monitoring offers the best description of dose received, exposure levels based on breathing zones are overestimated.

Some workers did receive an occasional acute exposure between 1954-1970. Ott et al., do not indicate if these employees were among the cancer deaths. Serum bromide concentrations taken since 1957 on a small number of men were considered too dependent on diet, medications, and drinking water bromide to be of value.

Industrial hygiene measurements were not utilized in the analysis: the level of exposure was based purely on duration of employment in the job categories of reactor operator and still operator in either plant, and foreman and lead burner in the Texas plant. In a later analysis by Ramsey et al., (1978), time-weighted averages from personnel monitoring (0.9 ppm) and from breathing zone samples (3.0 ppm) were used.

ANALYSIS

The number of deaths from all causes and from malignant neoplasms is shown in the lower half of Figure 1. Those persons who were exposed to both arsenicals and EDB were excluded from the analysis because arsenical exposure and respiratory cancer were found to be associated in a previous study (Ott et al., 1974). The two cancer deaths in this group had 1 1/2- and 20-month exposures to arsenicals, and respectively, 102 and 111 months exposures to EDB. Given the much longer exposure to EDB, one cannot rule out the possibility of an EDB effect, including a potential synergism of the two chemical exposures. Thus, these deaths should be considered in the analysis.

The overall mortality experience of the remaining 156 employees is close to expected rates (21 observed vs 19.5 expected for the Texas plant, 15 observed vs. 13.0 expected for the Michigan plant). Notably missing is any obvious "healthy worker" effect. Even cardiovascular deaths are not low, as they often are in working populations. The number of cancer deaths in the Texas plant was 2 where 3.6 were expected, a statistically nonsignificant difference, and in the

Michigan plant 5 were observed (7, including the arsenic-exposed), where 2.2 were expected. The value of five differs from 2.2 with a probability (p-value) of 0.06 meaning that under the assumption of no EDB effect such a difference could occur by chance 6% of the time. The other 94% of the time the assumption is false and the EDB-exposed workers have a higher cancer risk. Since we are only interested in differences where the risk is elevated (as seen in higher than usual numbers of deaths), the one tailed probability is 0.03. For the value of seven deaths, the (one tailed) p-value is 0.0006, meaning that the chances are 9994 out of 10,000 that the EDB-exposed have an elevated cancer mortality.

Confidence intervals have been calculated in three ways (see Table 2). The incidence proportion is defined as the number of deaths divided by the number of persons, and does not take into account years at risk, which varies from one individual to the next depending on how many years have passed since first exposure. The incidence rate is the number of deaths divided by the person-years at risk and is, therefore, a more refined measurement. After obtaining confidence limits for the rate or proportion, one multiplies by the persons or person-years at risk to yield the confidence limits for the number of deaths. The SMR confidence interval was derived by the method of Bailar and Ederer (1964) and multiplied by the expected number of deaths to find the confidence interval for the number of deaths. The three methods provide very similar results, and in all cases the expected number of deaths lies within the 95% confidence interval, except when the two workers exposed to arsenic are included in the Michigan plant deaths.

If one eliminates the 23 employees whose first exposure was less than 15 years before the study, the difference between the six observed deaths and the 4.3 expected is also not statistically significant ($p = 0.23$). The data indicate some degree of dose-response when dose is based purely on duration of exposure, though statistical significance was not reached (see Table 3). Given the probable inaccuracies inherent in this measure of exposure and the small numbers, the lack of statistical significance could have been anticipated.

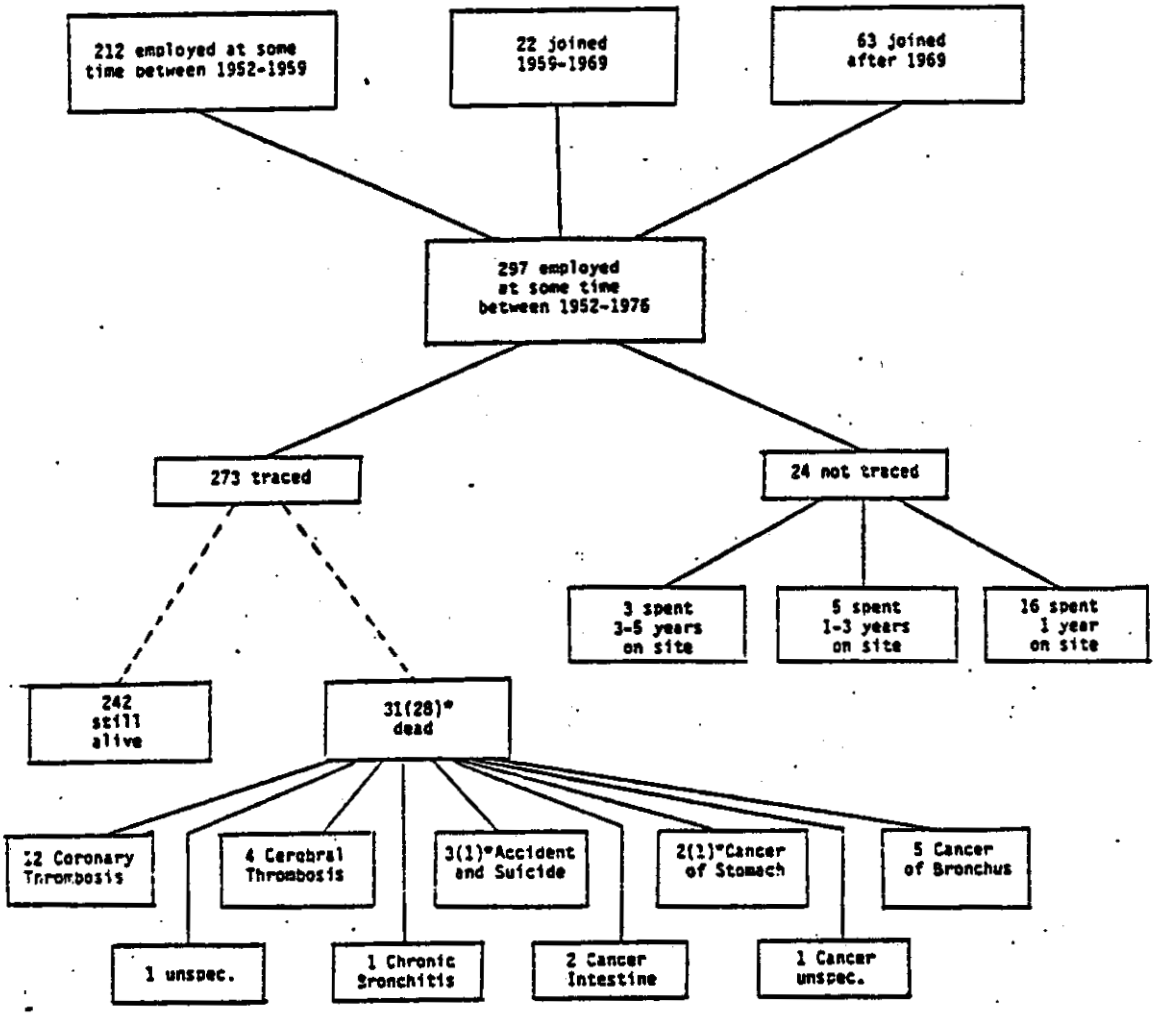
II. OTHER STUDIES OF OCCUPATIONAL EXPOSURES

Mortality studies of two other cohorts of occupationally exposed workers have been conducted but not published. These were submitted to OSHA by Dow Chemical USA in 1978 (DOL. 1981). These studies were conducted by D. Turner in Gwynedd, Wales (Amlwch plant) and Hayle, England (Associated Oct 4). No data on exposure were available for either plant.

The selection process for individuals at the Gwynedd plant is shown in Figure 2a. In actuality only those employed prior to 1960 were used in the analysis. The employees were medically examined prior to employment and represented a healthier than usual group. All employees were considered together; no distinction was made between those who may have had no exposure (e.g., managerial or clerical) and those who may have had heavy exposures.

FIGURE 2a

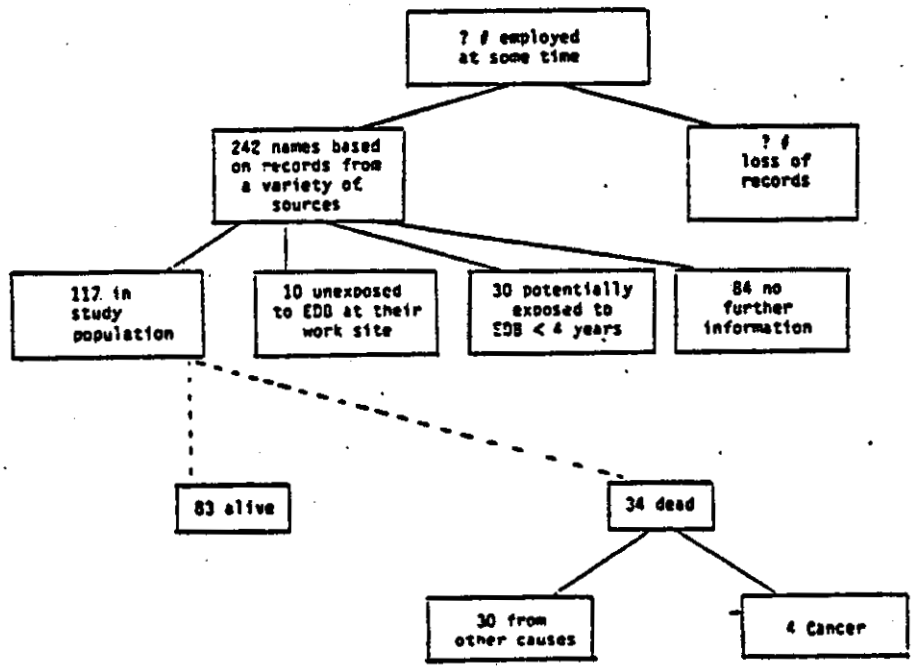
Selection Process for Employees for Study at Gwynedd, Wales (In operation 1952)



*Number of deaths in parentheses were among the original 212 employees and occurred after 1959.

FIGURE 2b

Selection Process for Employees for Study at Hayle, England (Produced EDB 1940-1970)



Death rates were calculated for the years 1960-75, but the denominator was calculated incorrectly: the author counted each individual for 16 years without subtracting for those who died during the interval. This changes the rates slightly: instead of the reported 2.7 cancer deaths per 1000 males, there were 3.1. This is still lower than the rate reported for the local region of Gwynedd, Wales, where males aged 45-64 experienced 3.7 cancer deaths per 1000 males. However, this rate (3.7 per 1000 males) is 1) larger than the comparable rate for England and Wales according to the local medical officer, and 2) based on an older age-grouping since the average age of the workers was 40-55 during those 15 years. It seems notable that of the nine specified cancers, six occurred in men aged 40-49. Among all the deaths, duration of employment averaged 13 years.

The selection of employees for study at the Hayle EDB manufacturing plant is shown in Figure 2b. Records were apparently poor for those who were employed during the war years only; however, for those employed since 1947 information on enployment (not follow-up) and potential exposure status was virtually complete. This investigation excluded those for whom no EDB exposure could have occurred.

The overall death rate, and the rate for cancer deaths, were computed for the age intervals 25-44, 45-64, 65-74, and 75+. These rates were not statistically different from those of southwest England in either 1961 or 1970, for the same age intervals.

In summary, the results for these two plants cannot be meaningfully evaluated since 1) no measurements of exposure levels were made, 2) the numbers of workers involved in other jobs or production processes where no exposure would have been incurred is unknown, especially at Amlwch, 3) no comparisons were made with the general British population of the same age, and 4) the loss to follow-up of 35% of the Hayle plant employees may have biased the results.

III. INTERPRETATION

The results of the three studies neither prove nor preclude a carcinogenic effect from occupational EDB exposure. In support of a carcinogenic effect:

1) the elevation of cancer mortality occurs where exposure data exists and where outcome data is the firmest, the one-tailed probability being $p=0.03$ for the number of observed deaths, or $p = 0.0006$ if an effect of EDB is assumed for the two employees who additionally were exposed to arsenic;

2) the evidence is suggestive of a dose response at the two U.S. plants.

For many reasons, the lack of strong epidemiologic evidence for carcinogenesis does not carry much weight;

1) The quality and quantity of exposure data is poor, even where it exists. While area sampling was done in Michigan on a continuous basis only during 1971-72, the range of measurements was wide, and only two measurements involved personal monitoring.

2) The degree of misclassification of employees' exposure is unknown, since a) at the U.S. plants longer duration of employment may not reflect greater exposures, and the turnover rate may have been greatest for those with the highest acute exposure, and b) the Gwyedd plant cohort may have included some employees with minimal or no exposure.

3) The sensitivity (statistical power) of the studies is low due to small sample size and the lack of sufficient follow-up for 23 employees at the Michigan plant.

On the other hand, it is entirely possible that inhalation of EDB does not have a carcinogenic effect on humans, or at least not at the doses to which workers are occupationally exposed. Any apparent effect might be explained by exposures to other known carcinogenic chemicals at the Michigan plant, which included benzene and carbon tetrachloride, or other unknown carcinogens.

TABLE 1

COMPARISON OF TWO EDB MANUFACTURING PLANTS

Unit 1 - Texas	Unit 2 - Michigan
1942 - 1969	1920's - 1976
No quantitative data	Quantitative data included: Area sampling (1950, '52, '71-'72. '75) of breathing zone, and after spills. Personnel sampling (1975) Blood bromide concentrations since 1957
Early 1960's change from batch to continuous reactors	
No other organic bromide products	Other organic halogens used/manufactured
Chemical exposures were: EBB bromine ethylene sulfur dioxide chlorine	Documented exposures to arsenic for some employees Chemical exposures for reactor operators were: EDB, bromine, ethylene, hydrogen, iodine, ammonia, silica, copper acetate, nickel acetate, vinyl bromide Direct chemical exposures for still operators were: trimethylene chlorobromide propylene chlorobromide ethyl bromoacetate isobutyl bromide acetylene tetrabromide Indirect exposures for still operators were: allyl chloride, benzene, bromochloromethane, carbon tetrachloride, chloroform, vinyl bromide, ethyl bromide, hydrogen bromide, methylene chloride, methylene dibromide, tert-bromobutyl phen, tert-butyl phenol
Reactor & distillation operations in same building	Reactor operation housed in a different building from distillation/drumming.

TABLE 2

95% CONFIDENCE INTERVALS FOR THE NUMBER OF CANCER DEATHS AT THE TWO U.S. EDB PLANTS

		95% Confidence Interval			
	Observed	Using Incidence Proportion [1]	Using Incidence Rate [1]	Using S.M.R.[2]	Expected[5]
Texas (99)	2	(.35, 7.73)	(.35, 8.05)	(.24, 7.22)	3.6
	3[3]	(.78, 9.15)	(.77, 9.54)	(.62, 8.77)	
Michigan (57)	5	(1.87, 11.42)	(1.84, 12.36)	(1.63, 11.68)	2.2
	7[4]	(3.13, 13.85)	(3.07, 15.07)	(2.81, 14.43)	
Total	7	(3.09, 14.65)	(3.07, 15.10)	(2.81, 14.43)	5.8
	10	(5.13, 18.42)	(5.08, 19.03)	(4.81, 18.38)	

[1] Confidence limits for small p (Fleiss 1981) multiplied by persons (incidence proportion) or person-years (incidence rate) at risk.

[2] Confidence limits of an SMR (Bailar and Ederer 1964) multiplied by the expected number of deaths.

[3] Includes 1 arteriosclerotic heart disease death in which carcinoma of lymph nodes was reported.

[4] Includes 2 deaths of workers exposed to both EDB and arsenic.

[5] Age-specific white male cancer mortality rates.

TABLE 3

CANCER INCIDENCE IN TWO U.S. PLANTS
AND LENGTH OF EXPOSURE TO EDB

DURATION OF EXPOSURE	INCIDENCE PROPORTION Cancer deaths Persons at risk	INCIDENCE RATE Cancer deaths Person-years at risk
< 1 year (.5)	0/31	0/ 722
1- 5 years (3)	3/84	3/1993
6-16 years (10)	4/46	4/1346
$x^2_{(1)}$	3.49	2.29
p	.07	>.1

APPENDIX C

COMPATIBILITY OF ANIMAL-BASED RISK ASSESSMENTS WITH EPIDEMIOLOGIC DATA

Ramsey et al. (1978) applied one of the first models used by the Carcinogen Assessment Group (CAG) of the Environmental Protection Agency (EPA, 1978) based on the NCI gavage bioassay data to predict risks for the cohort studied by Ott et al. Their results suggested a wide discrepancy between the model predictions from this model and the workers' experience. The Department of Health Services (DHS) has re-examined their figures and conducted its own analysis in order to determine the implications for human risk assessment.

I. The One-Hit Model

The model used by Ramsey et al. was a simple, one-hit, no threshold model. The model assumptions were as follows:

1). "Simple" refers to the fact that the timing of exposure is ignored; that is, the model utilizes total lifetime dose regardless of whether small exposures extended over a long period or acute doses were experienced in shorter intervals.

2). The one-hit model is based on the assumption that for the induction of carcinogenesis, an agent need cause only one heritable mutation in the DNA of a single cell.

3). Risk was estimated by the equation:

$$P = 1 - \exp(-Bd)$$

where B is a parameter for potency and d represents the total lifetime dose.

4). It is assumed that the dose-response curve exhibits no threshold, i.e., any exposure carries a non-zero probability of initiating cancer.

5). This model gives an estimate of risk for a total lifetime; therefore another factor was included to account for only partial lifetime observation of the workers. Since the probability of an agent inducing cancer before time t is influenced by age, another parameter "g" was estimated for the age-dependency of cancer risk. Thus the adjusted equation for risk is:

$$P = 1 - \exp[(-Bd)(age/70)^g]$$

The two parameters were calculated by CAG to be B = 31.73 and g = 6.95.

Ramsey et al. described the calculation of individual worker risks. The exposure assumptions were:

a. Dose was calculated as mg/(kg x day).

b. Weight was assumed to be 70 kg.

c. A work-year of 250/365 days.

d. Inspiratory volume of 14 m^3 per 8-hour working day.

e. Complete absorption via the lung.

f. Two possible time-weighted-average (TWA) exposure levels based on industrial hygiene samples. (In 1971-72 and 1975, area samples in one of the plants had TWA's ranging from 2.9 to 5.0 ppm while personal monitoring yielded TWA's of 0.8 to 1.1 ppm.)

By calculating the risk of an EDB-induced cancer death for each worker, and summing these, the application of this one hit model predicts for a population of 161 workers, 85 excess cancer deaths from an exposure of 3.0 ppm, or 54 excess deaths from 0.9 ppm exposure. A comparison of observed deaths to expected deaths based on U.S. white male age-specific rates, and deaths predicted by this model is shown in Table 1a. The total predicted deaths would be obtained by adding the U.S.A. expected background rate to the excess predicted from EDB exposure. Figure 1 graphically represents the number of excess deaths above U.S.A. expected levels. Predictions are shown for each plant for each of the two assumed exposure levels.

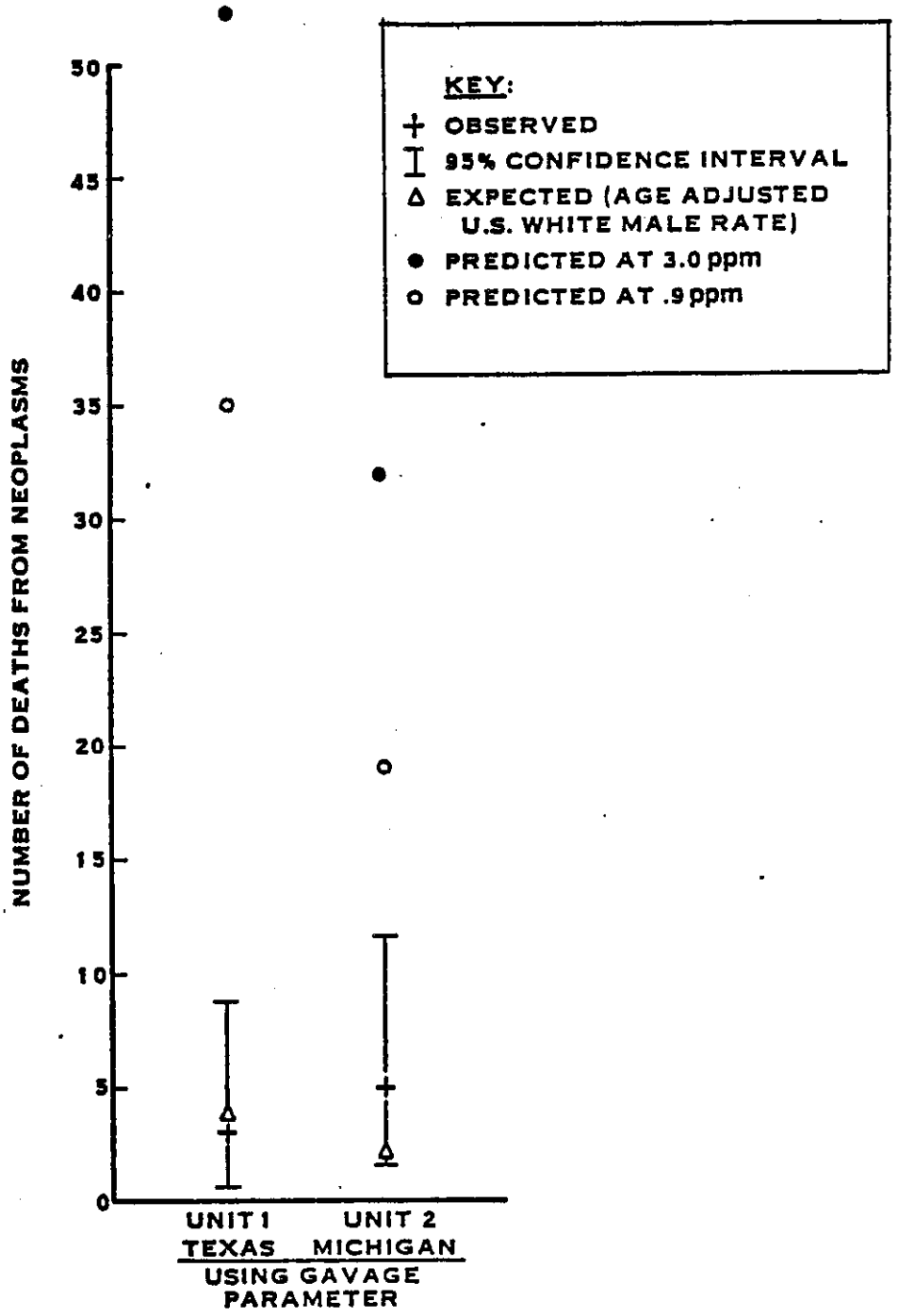


Figure 1. Observed cancer deaths compared to one-hit predictions. The one-hit model as employed by Ramsey et al predicts a number of cancer deaths so large that they lie above the upper 95% confidence limit for each of the two small populations of EDB workers studied.

It is clear from Table 1a and Figure 1 that the predictions are 4 to 19 times the observed deaths, very much beyond the 95% confidence intervals based on the observed deaths. Table 1b places the same information in the form of a standardized mortality ratio (SMR). The usual SMR is defined as:

$$\text{SMR} = \frac{\text{observed number of cancer deaths}}{\text{expected number of cancer deaths}}$$

The "predicted SMR" is analogously defined:

"Predicted" SMR =

$$\frac{\text{model-predicted number of excess cancer deaths + U.S.A. expected number}}{\text{U.S.A. expected number of cancer deaths}}$$

Also shown in this table is a calculation of minimum detectable SMR. This measures of the statistical power of the study by indicating how high the mortality would have to be elevated in order to have an 80% chance of seeing that degree of excess risk with the actual sample size of workers. The interpretation is as follows: if the model accurately represents the true human cancer risk, and if the exposure levels are a reasonable estimate of the actual doses received, then, since the predicted SMR was greater than the minimum detectable SMR, the size of the exposed work force was in fact large enough to detect the predicted rise in cancer mortality. Since no such elevation in cancer mortality was observed, this version of the one-hit model as used by Ramsey et al. is therefore not compatible with the mortality experience of the exposed workers.

II. Multistage and other models

DHS compared the observed deaths of workers in the Ott et al. study with predictions from the multistage model. Model assumptions were as follows:

1) Cancer induction is represented as a multi-stage process in which a series of heritable changes occur in the DNA, each change being a prerequisite for the next. Each change occurs as a linear function of dose and the result is a polynomial with coefficients estimated from the animal data.

2) As in the analysis by Ramsey et al., the total lifetime dose determines the magnitude of risk, irrespective of the timing of the dose.

3) No threshold is assumed (this need only be true for one stage).

4) The equation for the model is:

$$P = 1-\exp\left[-(B_1 d + B_2 d^2 + \ldots)\right]$$

The number of stages is mathematically limited to one less than the number of treatment groups in the experimental data.

5) In this case, a crude correction for partial lifetime observation was made, in which cancer mortality was assumed to be uniform throughout life and the mean age for the cohort was applied to all the workers. Thus predicted risk was (55/70) x P. (Results both with and without the correction are seen in Appendix D).

Exposure assumptions were the same as those made by Ramsey et al. except that (a) the inspiratory volume was estimated at 9.6 m^3 per 8-hour working day instead of 14, (b) dose was calculated as average daily lifetime ppm, and (c) exposure duration was based on the grouped data taken from Table 4 in the report of Ott et al. Subsequent calculations (not shown) utilizing individual worker data yielded risks that were essentially identical to those obtained with the grouped data.

Using the Global-79 software developed by K.S. Crump, risks were estimated based on nasal cavity malignancies in male rats in the NCI inhalation bioassay. Calculations of total risk based on individual risks estimated by the model are shown in Appendix D. Table 2 shows the predicted number of cancer deaths among the EDB-exposed workers in the Ott et al. study for a partial lifetime of observation. Figure 2 presents these figures graphically.

Several points can be made about these results.

As can be seen in Appendix D, the time-weighted average daily lifetime exposure of workers potentially ranged from an estimated 2 ppb for workers exposed to 0.9 ppm for half a year, to an estimated 268 ppb for workers exposed to 3 ppm for 16 years. This average daily exposure of workers over their total lifetime is much lower than the work time exposure. The multistage model uses the lifetime daily average exposure in predicting risks.

The multistage 95% UCL based on nasal malignancies predicts only a few cases among these 161 workers. The prediction is not much different from what was observed and falls well within the confidence intervals around the observations in this small study.

The 95% UCL extrapolated from the NCI inhalation bioassay using the multistage model and nasal malignancies in male rats is not incompatible with epidemiologic evidence and is, therefore, scientfically defensible as an upper limit of risk for purposes of risk assessment.

The Weibull-multistage model predictions based on the nasal tumors are also compatible with the epidemiologic results in that they too fall well within the confidence limits of the observed mortality, as would be any predictions based on the hemangiosarcomas, regardless of the three models we have used here.

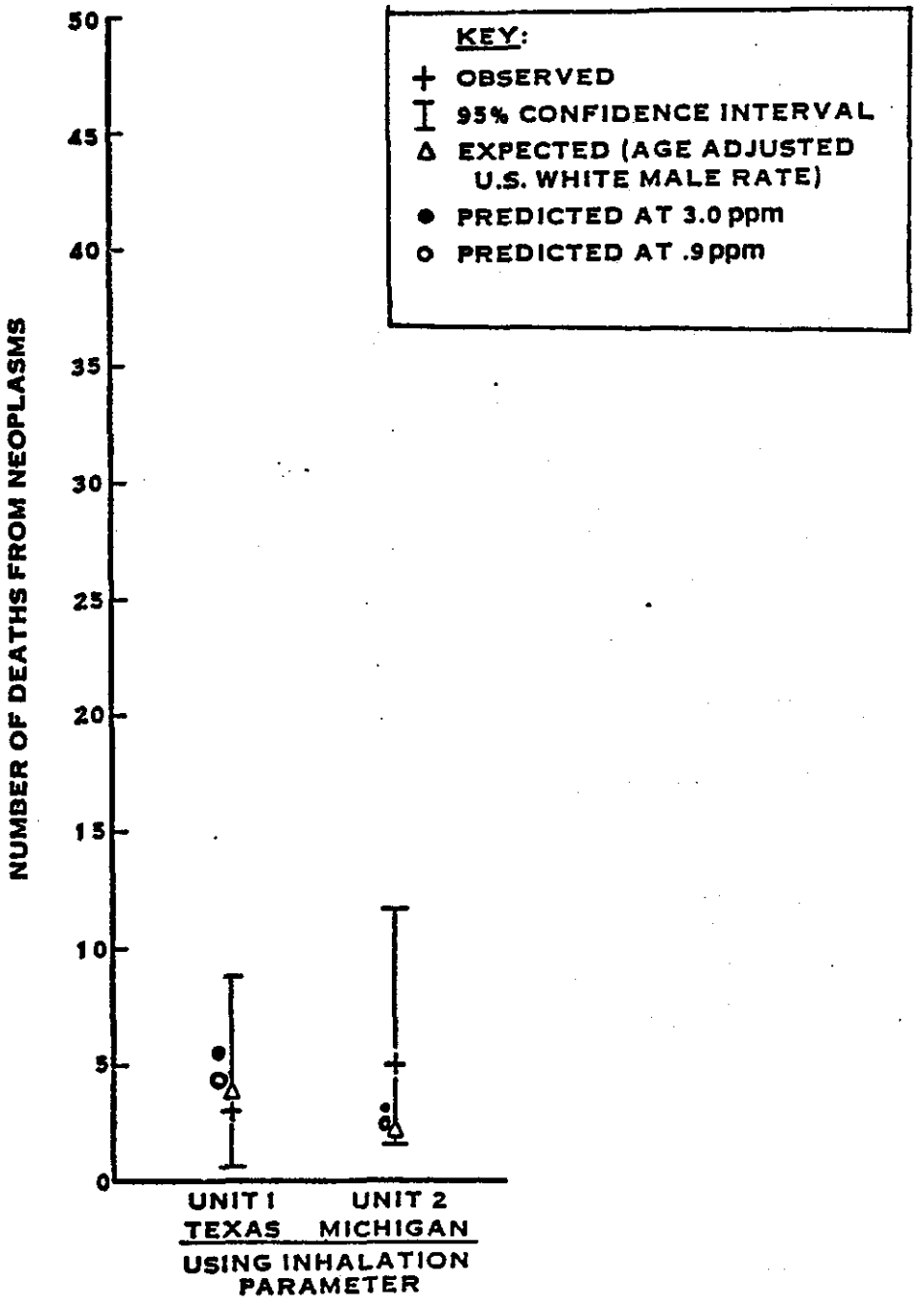


Figure 2. Observed cancer deaths compared to multistage model predictions. The multistage model as based on nasal malignancies predicts relatively few added cases of cancer in the small cohorts, well within the confidence limit for each of the two populations of EDB workers studied.

III. Factors responsible for the differences between DHS results for worker cancer risks and those published by Ramsey et al.

1. Choice of model

The multistage model allows for up to 2 stages given 3 dose levels in the animal bioassays, but the best fit was given by a linear function of dose; thus the multistage model in fact reduced to a one-hit model when nasal malignancies in rats or hemangiosarcomas in mice were used. Hence the choice of model cannot explain the differences between Ramsey's conclusion and that of DHS.

2. Exposure assumptions

The DHS assumed inspiratory volume to be 9.6 m^3/8-hr working day, while Ramsey et al assumed it to be 14 m^3/8-hr working day. The substitution of 14 m^3 in the DHS model increases the predicted risks to workers by about 1.5 (Texas plant, 2.87 excess deaths; Michigan plant, 1.55 excess deaths, at the higher exposure level). These predictions are still well within the confidence intervals.

3. Gavage vs. inhalation

At first sight it appears that the difference is due to the use by Ramsey et al. of gavage bioassay data while DHS used the inhalation data. However, if the data on stomach tumors from the gavage study are used directly (without adjusting for the early mortality as was done by

CAG), the coefficient (slope) fit by the multistage model is practically identical to the coefficient fit by using the data on nasal malignancies from the inhalation study. Thus the predicted risks based on the unadjusted gavage data would be essentially the same as those based on the inhalation data.

4. Adjustment for early mortality

The severe early mortality in the gavage study required adjusting the data from the bioassay prior to estimating the model's parameters. Since survival was reasonably good in the inhalation study, even for the high dose group, this was not necessary for the analysis performed here. It appears, therefore, that the adjustment for early mortality in the gavage study is responsible for the difference between the results obtained by Ramsey et al. and those of the DHS. However, it is difficult to separate the effects of this adjustment from the effects of the two different routes of exposure. It is possible that EDB is less potent via inhalation than it is via gavage administration.

IV. Conclusion

DHS staff has confirmed the conclusion of Ramsey et al. that the use of the one-hit model, with parameters estimated from gavage data adjusted for early mortality, to predict cancer mortality in the study of Ott et al. produces results which are not compatible with the epidemiology in that they are too high by far.

Staff of DHS applied the multistage model (Crump Global 79) to the same study of Ott et al. using the nasal carcinoma data from the NCI bioassay. The estimated excess risk using this model with a lifetime-averaged exposure is only a few extra cases of cancer, well within the confidence limits of the observed results. Another way of saying this is that the multistage model would predict an SMR close to that which was observed and that the power of Ott et al. study was not great enough to distinguish this from an SMR which indicated no effect of EDB, namely an SMR of 1.00.

The MLE and UCL estimates of the other models presented in the body of this document are also compatible with the study of Ott et al.

In pointing this out, DHS is not proposing that the Crump multistage model is generally superior to other models but simply that, when applied to epidemiological exposure data according to standard practice, it does not predict implausibly high numbers of cases from workplace exposure. This is an important point because the results of Ramsey et al. have at times been interpreted to mean that all EDB risk assessments are incompatible with the epidemiological data and that the Ott et al. study suggests that EDB poses no risk to humans even at occupational levels. The preceding analysis shows that the study of Ott et al. cannot be used to rule out the Crump multistage or the Weibull-multistage predictions, much less demonstrate the absence of an effect.

TABLE 1

One-Hit Model
Prediction of Worker Cancers
(Based on Gavage Study)

1a. Comparison of number of neoplasm deaths

	Number of neoplasm deaths			
	Observed (95% CI)	U.S.A. Expected[1]	Excess Predicted[2] 3.0 ppm	.9 ppm
Texas Unit 1	3(.62-8.77)[3]	3.6	53	35
Michigan Unit 2	5(1.63-11.68)	2.2	32	19

1b. Comparison of Standard Mortality Ratios (SMRs)

	SMR				
	Observed (95%CI)	U.S.A. Expected	Predicted[5] 3.0 ppm	.9 pm	Minimum Detectable[4]
Texas Unit 1	.83(.17-2.44)[3]	1.0	15.72	10.72	4.5
Michigan Unit 2	2.27(.74-5.31)	1.0	15.55	9.64	6.6

1. From U.S. white male age-specific mortality rate
2. Predicted by CAG model due to EDB exposure
3. Ramsey et al included one arteriosclerotic heart disease death with lymph node malignancy
4. Sample size has 80% power to detect an SMR this large (see text) (Schlesselman)
5. Predicted SMR = $\frac{\text{model predicted excess cases + USA expected cases}}{\text{USA expected cases}} = \frac{53 + 3.6}{3.6} = 15.72$

Table 2

Multistage Model Prediction
of Worker Cancer
(Based on nasal malignancies in NTP inhalation study)

2a. Comparison of number of neoplasm deaths

	Number neoplasm deaths			
	Observed (95% CI)	U.S.A. Expected[1]	Excess Predicted[2] 3.00 ppm	0.9 ppm
Texas Unit 1	3(0.62-8.77[3])	3.6	2.15	0.57
Michigan Unit 2	5(1.63-11.68)	2.2	1.13	0.25

2b. Comparison of SMR

	SMR				
	Observed (95% CI)	U.S.A. Expected[1]	Predicted[2] 3.0 ppm	0.9 ppm	Minimum Detectable[4]
Texas Unit 1	0.83(0.17-2.44)	1.0	1.6	1.16	4.5
Michigan Unit 2	2.27(0.74-5.31)	1.0	1.51	1.11	6.6

1. From U.S. white male age-specific mortality rates
2. Crump Global 79 multistage model
3. Ramsey et al included one arteriosclerotic heart disease death with lymph node malignancy
4. Sample size has 80% power to detect an SMR this large (see text) (Schlesselmen)

APPENDIX D
Estimated Total Excess Cancer Risk To Workers
Based on Nasal Cavity
Malignancies using the Simple Multistage Model

I. Interspecies Scaling

The method of interspecies extrapolation for inhalation of lipid soluble substances has been described previously (Part B, "Health Effects of Benzene") and is provided in the following paragraphs. Simple exposure equivalency using a scaling factor of 1 (ppm) was used. This is possible due to the assumption that surface area provides the best scaling factor between species. Direct exposure equivalency is derived from this assumption since inhalation volume is a function of surface area.

"The dose in mg/kg of partially soluble vapors is proportional to oxygen consumption, which in turn is proportional to $W^{2/3}$ and is also proportional to the solubility of the gas in body fluids, which in turn can be expressed as an absorption coefficient, r, for the gas. Therefore, expressing the O_2 consumption as $O_2 = (k)\ (W^{2/3})$, where k is a constant independent of species, it follows that:

If:

m - the average dose/day in mg during administration of the agent.

v - the average lifetime concentration of benzene in the inhalation chambers,

then:

$$m = (k) \times (W^{2/3}) \times (mg/m^3) \times r$$

$$\text{dose} = \frac{m}{W^{2/3}} = kvr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction, r, is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or in mg/m^3 in experimental animals is equivalent to the same concentration in humans (Part B, "Health Effects of Benzene")".

II. Calculations

Step 1: Conversion of worker exposure of 0.9 and 3.0 ppm for 1 year to lifetime time-weighted average (TWA) equivalent.

Assume:
- 9.6 m^3 air breathed over 8 hours
- 20.0 m^3 air breathed over 24 hours
- 5 work days per week
- 46 work weeks per year
- 55 as average age of worker

$$\text{3.0 ppm for 1 year} = (3 \text{ ppm}) \times \frac{(9.6 \text{ m}^3)}{(20 \text{ m}^3)} \times \frac{(5 \text{ days})}{(7 \text{ days})} \times \frac{(46 \text{ weeks})}{(52 \text{ weeks})} \times \frac{(1 \text{ yr})}{(55 \text{ yr})}$$

$$= (3 \text{ ppm}) \times (.00551)$$

$$= .0165 \text{ ppm}$$

$$= 16.5 \text{ ppb time weighted exposure over a lifetime}$$

$$\text{0.9 ppm for 1 year} = (.9 \text{ ppm}) \quad (.00551)$$

$$= .00496 \text{ ppm}$$

$$= 4.96 \text{ ppb time weighted exposure over a lifetime}$$

Step 2: Estimating Risk From Animal Data

The multistage model was used to estimate risk from a time-weighted lifetime exposure from 1 ppb. NCI inhalation data on male rats were used. Risk from nasal cavity malignancies: adenocarcinomas, squamous cell carcinomas, and carcinomas (NOS).

Though high and low dose rats were exposed to 40 ppm, and 10 ppm respectively, this was only for 6 hours per day and 5 days per week. The time-weighted average ppm for both groups was calculated as follows.

$$40 \text{ ppm} \times \frac{6}{24} \times \frac{5}{7} = 7.14 \text{ ppm}$$

$$10 \text{ ppm} \times \frac{6}{24} \times \frac{5}{7} = 1.79 \text{ ppm}$$

The multistage model was then provided the following data entry table.

	Dose	Animals	Malignancies
Control	0	50	0
Low	1.79 ppm	50	23
High	7.14 ppm	50	38

The resulting best fit model was:

$$r = 1 - e^{-(0 + 0.253 \text{ dose})}$$

where dose was entered as ppm

The 95% UCL for lifetime risk at 1 ppb was 3.15×10^{-4}

The 95% UCL of 3.15×10^{-4} was used to see if it was incompatible with the epidemiological data. This is the multiplier in column D of the next step.

Step 3: Total Excess Risk for Workers at 0.9 ppm TWA Exposure Estimated from Simple Multistage d Model and Nasal Cavity Malignancies in Mice and Rats

A	B	C[1]	D[2]	E[3]	F[4]	G[3]	H[4]
		ppb Equivalent Lifetime Exposure	95% UCL for MLE of Risk for Life-time Exposure	UNIT 1*		UNIT 2*	
Worker Years	Assumed Worker Years	(Col. Bx4.96)	($3.15x10^{-4}$ x Col. C)	Total Workers	Total Excess Risk (Col. D x E)	Total Workers	Total Excess Risk (Col. D x G)
0-1	0.5	2.48	$7.82x10^{-4}$	24	$1.88x10^{-2}$	7	$5.47x10^{-3}$
1-5	3.0	14.89	$4.69x10^{-3}$	45	$2.11x10^{-1}$	39	$1.82x10^{-1}$
6-10	8.0	39.70	$1.25x10^{-2}$	10	$1.25x10^{-2}$	11	$1.38x10^{-2}$
11-15	13.0	64.52	$2.03x10^{-2}$	5	$1.02x10^{-1}$	3	$6.09x10^{-1}$
16.0	16.0	79.42	$2.5x10^{-2}$	15	$3.75x10^{-1}$	2	$5.00x10^{-2}$
		Total Excess Risk:		99	$7.19x10^{-1}$	62	$3.12x10^{-1}$
		Total Risk to age 55:			$5.65x10^{-1}$		$2.45x10^{-1}$

1. (Assumed worker years) x (Time-weighted average from Step 1. Exposure for 1 year).
2. (Equivalent Lifetime Exposure) x (Upper 95% CL at 1 ppb) nasal cavity malignancies at 1 ppb. Simple Multistage Program, NCI male rats.
3. Number of workers by exposure durations from Ott et. al., Table 4.
4. (Excess risk per worker at exposure) x (Number of exposure years).

* Unit 1 = Texas plant
Unit 2 = Michigan Plant

Step 4: Total Excess Risk for Workers at 0.9 ppm TWA Exposure Estimated from Simple Multistage Model and Nasal Cavity Malignancies

A	B	C[1]	D[2]	E[3]	F[4]	G[3]	H[4]
		PPB Equivalent Lifetime	95% UCL for MLE of Risk for life-	UNIT 1*		UNIT 2*	
	Assumed	Exposure	time Exposure	Total	Total Excess	Total	Total Excess 5
Worker Years	Worker Years	(Col. Bx16.5)	(3.15×10^{-4} x Col. C)	Workers	Risk (Col. D x E)	Workers	Risk ICol. D x G)
0-1	.5	8.27	2.61×10^{-3}	24	6.26×10^{-2}	7	1.83×10^{-2}
1-5	3.0	49.63	1.54×10^{-2}	45	6.93×10^{-1}	39	6.01×10^{-1}
6-10	8.0	132.35	4.11×10^{-2}	10	4.11×10^{-1}	11	4.52×10^{-1}
11-15	13.0	215.06	6.67×10^{-2}	5	3.34×10^{-1}	3	2.00×10^{-1}
16.0	16.0	264.7	8.21×10^{-2}	15	1.23	2	1.64x10
		Total Excess Risk:		99	2.73	62	1.44
		Risk to age 55:			2.15		1.13

1. (Assume worker years) x (Time-weighted average from Step 1. Exposure for 1 year).
2. (Equivalent lifetime exposure) x (Upper 95% CL at 1 ppb) cavity malignancies at 1 ppb. Simple Multistage Program NCI male rats.
3. Number of workers by exposure durations from Ott et. al., Table 4.
4. (Excess risk per worker at exposure) x (Number of exposure years).

* Unit 1 = Texas plant
Unit 2 = Michigan plant

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