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Review of Selected Literature on Ethylene Dibromide (EDB)

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REVIEW OF SELECTED LITERATURE ON ETHYLENE DIBROMIDE (EDB)

JUNE 1976

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

EPA-560/8-76-001

REVIEW OF SELECTED LITERATURE
ON
ETHYLENE DIBROMIDE (EDB)

Prepared by

Office of Toxic Substances
Environmental Protection Agency
Washington, D.C. 20460

June 1976

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16. ABSTRACT

Ethylene dibromide (synonyms - 1,2-dibromoethane; ethylene bromide; and EDB) is a synthetic organic chemical used mainly as a lead scavenger in leaded gasoline antiknock preparations to volatilize the lead so that it is not deposited on engine surfaces during combustion.

Annual production of ethylene dibromide averaged about 300 million pounds in the period 1969 to 1974. A decrease in production to 280 million pounds occurred in 1970 and 1971. An upward trend is apparent from the preliminary figures for 1972 (315 million pounds) and 1973 (331 million pounds). Estimated consumption as a fuel additive is about 80 percent of production. A relatively small amount, about 1.5 to 2 million pounds, are accounted for as pesticides. As a result of the expected decline in the use of lead in gasoline, and use of EDB as a lead scavenger is also expected to decline.

Animal experimentation demonstrates that ethylene dibromide is a highly toxic material with anesthetic and strong irritant properties. Under chronic exposure liver and kidney involvement is observed. Carcinogenic activity has been reported for two species after chronic oral exposure. Mutagenic potential has also been associated with EDB under certain test regiments. Reproductive effects in bulls have been noted after oral exposure. Adverse effects on egg production are observed in laying hens fed EDB treated grain.

The principal use of EDB is consumptive and amounts entering the environment cannot be readily estimated. Very limited and preliminary air monitoring data suggest EDB is present in ambient air at very low concentrations.

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a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
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Abstract

Ethylene dibromide (synonyms - 1,2-dibromoethane; ethylene bromide; and EDB) is a synthetic organic chemical used mainly as a lead scavenger in leaded gasoline antiknock preparations to volatilize the lead so that it is not deposited on engine surfaces during combustion.

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Animal experimentation demonstrates that ethylene dibromide is a highly toxic material with anesthetic and strong irritant properties. Under chronic exposure liver and kidney involvement is observed. Carcinogenic activity has been reported for two species after chronic oral exposure. Mutagenic potential has also been associated with EDB under certain test regiments. Reproductive effects in bulls have been noted after oral exposure. Adverse effects on egg production are observed in laying hens fed EDB treated grain.

The principal use of EDB is consumptive and amounts entering the environment cannot be readily estimated. Very limited and preliminary air monitoring data suggest EDB is present in ambient air at very low concentrations.

Properties

Ethylene dibromide (EDB) is a colorless, heavy, nonflammable liquid with a sweet odor. The odor is detectable at 10 ppm (NIOSH, 1975).

Chemical and physical data are shown in Table 1.

Table 1 (Merck Index, 8th Ed.)

Empirical formula:	$BrCH_2CH_2Br$
Molecular weight:	187.88
Boiling point:	131-132^{o}C
Appearance:	colorless liquid
Vapor pressure:	17.4 mm Hg @ 30^{o}C
Specific Gravity:	$d\frac{25}{25} = 2.172$
Solubility :	miscible with most solvents; slightly soluble in water

Uses

EDB's major use is as a gasoline additive (SRI estimates 80 percent of production). It serves as a lead scavenger in leaded gasolines either alone or in combination with ethylene dichloride (EDC). Lead antiknock compositions containing ethylene dihalides as scavenging agents typically contain enough to supply one atom of halogen for each atom of lead. Halogen-containing compounds typically cause a decrease in the octane number of leaded gasolines. EDB and ethylene dichloride are used because they are the least expensive organic halides which do not reduce the antiknock effectiveness of lead alkyls. At present the trend is to increase the ethylene dichloride in the mixture. The cost of ethylene dichloride is about one third that of EDB. While automotive gasoline contains both EDB and ethylene dichloride, aviation gasoline contains EDB alone. Ethylene dichloride is not used alone probably due to a lower functional efficiency than EDB.

Over 124 pesticides containing EDB are registered with EPA. About 1.5 to 2 million pounds of EDB are used annually for agricultural purposes, such as a fumigant on many crops, particularly grains and fruits (EPA, 1975). Many EDB containing fumigants also contain ethylene dichloride, carbon tetrachloride or methyl bromide. Soil fumigant nematocides containing EDB usually also contain methyl bromide.

Ethylene dibromide is also used as an intermediate in the synthesis of dyes and pharmaceuticals, and as a solvent for resins, gums and waxes. A minor use of EDB with considerable growth potential is as a chemical precursor for vinyl bromide.

Production

Ethylene dibromide is prepared commercially by reacting bromine with ethylene gas. The major U.S. producers are Ethyl, Dow, PPG, Northwest and Great Lakes. Four EDB manufacturing sites are located in Arkansas with one in Texas and another in Michigan. Salient statistics available for ethylene dibromide are shown in Table 2.

Environmental Aspects

Fresh water toxicity data for EDB is reported in ENVIRON (1974). The 48-hour TLm for bluegill and largemouth bass are 18 and 15 ppm, respectively. (TLm (tolerance limit median) represents the dose that kills 50 percent of the animals for the time period indicated).

In studies on the behavior of EDB in soils McKenry (1972) observed that EDB did not degrade to any great extent after a two week period. But, Castro and Belser (1968) found that in soil-water culture (sterilized soil that was inoculated) EDB at 5.75×10^{-4}M converted almost completely and quantitatively in about two months (see Figure 1).

Table 2 - Ethylene dibromide production, imports, sales

Production[a]	Million lbs.
1969	309.9
1970	296.8
1971	280.0
1972	315.5
1973	331.1
1974	332.1
Imports[a]	**Million lbs.**
1966	0.519
1967	0.185
1968	0.002
1969	0.058
1970	0.084 (last year reported)
Sales[a]	
1969	-
1970	145.6
1971	173.7
1972	173.4
1973	169.3
1974	170.8

a) International Trade Commission Reports (formerly U.S. Tariff Commission Reports)

Figure 1

$$BrCH_2CH_2Br \xrightarrow[\text{pH 7.0}]{\text{soil-}H_2O} CH_2{=}CH_2 + 2\ Br^-$$

Some very limited and preliminary air monitoring data shows air concentration values of 0.07-0.11 μg/m^3 (about 0.01 ppb) in the vicinity of gasoline stations along traffic arteries in three cities (Phoenix, Los Angeles, and Seattle), 0.2-1.7 μg/m^3 (about 0.1 ppb) on the property of an oil refinery in Kansas City, and 90-115 μg/m^3 (10-15 ppb) at EDB manufacturing sites in Arkansas. This suggests that EDB is present in ambient air at very low concentrations. Concentrations on the order of 1 ppb of EDB were found in two samples from streams of water on industrial sites (EPA, 1975a).

Sampling and Analysis Methodology

The EDB air monitoring data was obtained with an adsorbent technique using Tenax-GC® traps cooled with dry ice; recovery after two hexane extractions was about 95 percent. After collection, samples were stored in a freezer at -13°C. Analysis was by GC-ECD on Carbowax 20M. Additional columns were used for confirmation of identity. Water samples were extracted with hexane and stored in a freezer until analysis by GC-ECD (EPA, 1975a).

Methods for determining EDB content of gasoline engine exhaust have not been developed. However, methods developed for determination of halide scavengers in gasoline may be adaptable. GC with flame ionization detection has been used (Soulages, 1966; 1967). Another method is based on the quantitative conversion of EDB to vinyl bromide plus potassium bromide after reaction with alcoholic KOH (Esposito, 1972).

EDB Emission Estimates

EDB's major use as a gasoline additive is considered to be consumptive so that attention has been focused on EDB's potential for entry into the environment from evaporative and refueling losses and from its other uses.

Possible emission factors from lead scavenger uses include refueling and evaporative losses as well as automotive exhaust emissions. A "worst-case" and "most-likely-case" analysis was prepared by EPA's Office of Mobile Source Air Pollution Control. The estimated emission factors are contained in Table 3. Total amounts of EDB emitted can be approximated by multiplying the table values by the lead content (in gm/gal) of gasoline to obtain the EDB factor per gallon of fuel dispensed and then multiplying by the number of gallons of gasoline being dispensed.

In 1973 approximately 100 billion gallons of gasoline were consumed for highway use (CEH, 1975). The "worst-case" estimates reflect the fact that the exhaust emission factor for EDB is not well established experimentally; thus the assumption for those estimates was that 70 percent of the EDB in gasoline is emitted in the exhaust (EPA, 1975b).

Biological and Toxicological Considerations

EDB acute oral toxicity is moderate. Some reported LD_{50} values (Rowe *et al.*, 1952) are:

Mice (F)	420 mg/kg
Rats (M)	148 mg/kg
Rats (F)	117 mg/kg
Guinea pigs	110 mg/kg
Chicks	79 mg/kg
Rabbits (F)	55 mg/kg

Acute inhalation studies in rats (Rowe *et al.*, 1952) revealed immediate CNS depression (anesthesia, usually followed by death). Also observed was congestion, edema, hemorrhage, and inflammation of the lungs; swelling and necrosis of the liver and congestion and edema of the kidneys. Rats and guinea pigs survived for only a few hours at 200 ppm. Higher concentrations caused death in less than one hour.

Chronic inhalation studies (Rowe *et al.*, 1952) with rats and rabbits (7 hr/day for 5 days/wk for 6 mo.) at 100 ppm resulted in some deaths in less than 2 weeks. At 50 ppm about 50% of the rats died from pneumonia and upper respiratory infections due the effects of EDB. At 25 ppm rats,

Table 3. AUTOMOTIVE EDB EMISSIONS (EPA, 1975b)

	Controlled Vehicle		Uncontrolled Vehicle	
	g/gPb/gal.	g/mile 1/	g/gPb/gal.	g/mile 1/
Refueling Losses				
Spillage	0.000047	0.000005	0.000047	0.000005
Entrainment	0.000047	0.000005	0.000047	0.000005
Displaced vapor	0.000063	0.000007	0.000063	0.000007
Evaporative Losses				
Tank	0.00014	0.000016	0.00063	0.000042
Carburetor				
Most Likely	0.0016	0.00019	0.0028	0.00532
Worst Case	0.0043	0.00051	0.0076	0.000902
Exhaust Emissions				
Most Likely	0.0065	0.000771	0.019	0.002256
Worst Case	0.3	0.035625	0.3	0.035625
Total Emissions				
Most Likely	0.008397	0.000997	0.022317	0.002650
Worst Case	0.304597	0.036170	0.308117	0.036588

1/ Assumes average regular gas lead content of 1.90 grams per gallon and 16 miles per gallon.

guinea pigs, rabbits and monkeys generally tolerated the exposure without evidence of adverse effect as judged by general appearance and behavior, growth, final body and organ weights, blood urea nitrogen values, results of periodic hematological examination, and results of gross and microscopic examination of tissues; the highest mortalities were observed in rats due to pneumonia and upper respiratory infections.

A dose of 1.1 g/kg applied to the skin of rabbits killed 5 of 5 animals after a 24 hour contact period. Fourteen of fifteen animals survived a dose of 0.21 g/kg. (Rowe et al., 1952).

Laying hens fed 10 ppm EDB in grain resulted in gradual diminution of egg size and egg number. Alumot and Harduf (1970) in some isotope studies observed impaired passage of proteins from blood serum to ovarian follicles in EDB treated hens and indicate that this may be related to the decreased egg size observed in laying hens exposed to EDB in their diet.

Calves administered a single oral dose (gelatin capsule) of 10 or 25 mg/kg EDB suffered no ill effects. At 50 mg/kg EDB the calf died in three days, after signs of anorexia and prostration. Necropsies were inconclusive regarding gross lesions (Schlinke, 1969). Similar results were observed with sheep at the same dose levels. However, one sheep succumbed at the 25 mg/kg EDB dose (Schlinke, 1969).

Human Toxicity

Direct contact with EDB causes irritation and injury to the skin and eyes. Exposure to the vapor has caused the development of respiratory tract inflammation along with anorexia and headache with recovery after discontinuance of exposure.

Weakness and rapid pulse have been associated with EDB exposure as well as cardiac failure leading to death. (Von Oettingen, 1958 cited in NIOSH, 1975).

A case of accidental poisoning with 4.5. ml EDB in a 45 year old woman fatal after 54 hours. Primary pathological findings were liver necrosis and kidney tubular damage (Olmstead, 1960).

To date, there have been no published reports of any association between EDB and cancer in humans.

Mutagenic Potential

Several studies have shown EDB to have mutagenic potential. In a host-mediated assay in mice reported by Buselmaier et al., 1972, EDB was described as distinctly mutagenic at 500 mg/kg (subcutaneous dose).

In an ochre mutant, induced by hydroxylamine, Tessman (1971) observed a 7-fold increase in the number of reverse mutants over the background level after treatment with EDB. A study of AD-3 mutants from *Neurospora crassa* after treatment with EDB in solution of 10% DMSO (dimethyl sulfoxide) for 3 hours resulted in 1139 AD-3 mutants compared to 7 with 10% DMSO alone. (De Serres, 1970). Mutagenesis assays (Ames method) of a series of haloalkanes using *Salmonella typhimirium* showed EDB to be mutagenic. In addition, DNA-modifying effects were implied when EDB was shown to preferentially inhibit the growth of DNA polyermase-deficient (pol A^{-1}) *Escherichia coli* (Brem et al., 1974). Mutagenic activity as a result of EDB treatment has also been observed in *Drosophila melanogaster* (Vogel and Chandler, 1974).

Reproductive Effects

A study of sperm smears prepared from different parts of the genital tract of bulls after oral treatment with EDB (4 mg/kg on alternate days, for 12 and 21 days) showed a distribution of abnormal spermatozoa, which indicated the EDB affected the spermatozoa during spermatogenesis and during maturation in the epididymis (Amir, 1973).

Carcinogenic Activity

Gastric intubation of EDB to rats (40 and 80 mg/kg/day) and mice (60 and 120 mg/kg/day) 5 times per week resulted in a high incidence of squamous cell carcinomas of the stomach in both species as early as 10 weeks after initiation of treatment. The tumors originated locally in the forestomach, invaded locally, and eventually metastasized throughout the abdominal cavity. No squamous cell carcinomas were observed in controls (Olson et al., 1973). The "memorandum of alert" (10/4/74) by Page of NCI apparently describes the same study, characterizing the results which indicate strong carcinogenic activity as preliminary (see Appendix A). This document indicates that further tabulation and analysis of the data will be forthcoming after completion in November 1974.

Recent discussion with the National Cancer Institute (NCI) revealed that it will be several months before the final technical report on this study is issued. However, it was indicated that in fact the data are the same as that previously reported by Olson et al. (NCI, 1975).

NCI has developed the protocol for an inhalation carcinogenesis bioassay of EDB. The protocol specifies administration of EDB at the Maximum Tolerated Dose (MTD) and a fraction of the MTD. This study is presently in the planning stage (NCI, 1975).

Human Exposure-Occupational

The National Institute of Occupational Safety and Health has developed estimates of the worker population exposed to EDB (see Table 4).

Regulations

Many food tolerances have been established for inorganic bromide residues resulting from the use of EDB as a soil fumigant (40 CFR 120.126) and as a commodity fumigant (40 CFR 120.126). Food additive

Table 4. Estimated number of workers Exposed to Ethylene Dibromide by Industry* (Lloyd, 1975)

Industry	No. Exposed
Fumigators and Exterminators	8,897
General Merchandising	110
Chemical Manufacturing	76
Petroleum and Products Manufacturing	28
Total	9,111**

*Projections based on preliminary data from the National Occupational Hazard Survey, Hazard Surveillance Branch, Office of Occupational Health Surveillance and Biometrics, NIOSH. This does not include exposure to trade name products.

**Does not include approximately 650,000 persons employed in service stations with potential exposure to leaded gasoline.

tolerances of 125 ppm have been established for inorganic bromide residues in all processed food except for dried eggs (400 ppm) roquefort and parmesan cheese (325 ppm) and tomato products and dried figs (40 CFR 121.1020 and 121.270).

Use of EDB as a fumigant can also result in organic bromide residues. The quantities found are variable and dependent on many factors. In comparison studies with other fumigants EDB was found (in grains) in a range from less than 0.01 ppm to 6.10 ppm. The lower volatility of EDB compared to other commonly used compounds seems to account for the disproportionately higher residues. There is an exemption from the requirement of tolerance for organic bromide residues from EDB (40 CFR 120.1006) for the postharvest use on grains. The exemption was based on the conclusion that no residues of EDB results in food as consumed and that any residues are expelled by cooking (McMahon, 1971). However a Dutch study of EDB residues in wheat, flour, and bread, showed about 2-3 ppm EDB in flour from wheat fumigated with an EDB-containing fumigant 13 weeks earlier. Bread from this flour contained about 0.02-0.12 ppm EDB (Wit et al., 1969). EDB has been measured as a residue in fumigated commodities (Malone, 1971).

The current OSHA standard is 20 ppm EDB for an eight-hour-time weighted average with a 30-ppm acceptable ceiling concentration and an acceptable maximum peak of 50 ppm for a maximum duration of 5 minutes during an eight-hour shift. This is based on ANSI standard - Z.37.31 (FR 37 (202) p. 22139).

EDB Substitutes

Ethylene dichloride (EDC) is at least a partial substitute for EDB as a lead scavenger. The typical scavenger mix contains both EDB and EDC. EDB is considered to be functionally more efficient than EDC. The feasibility of EDC as a total substitute is uncertain.

Some toxicity information is available on EDC. The oral LD_{50} in rats is 0.68 g EDC/kg (McCollister et al., 1956). Health effects observed in guinea pigs after inhalation exposures to EDC were principally congestion and edema of the lungs. The kidneys showed congestion and degenerative changes (Sayers et al., 1930). At doses of 3000 ppm EDC in rats, pathological changes in the liver and adrenals were also observed (Spencer et al., 1951).

Chronic inhalation studies in rats at 200 ppm (151 exposures 7 hrs/day for 5 days/week for 212 days) showed no adverse effects. Similarily at 100 ppm, rats, guinea pigs, rabbits and monkeys were given 120 exposures for 168 days without apparent effect (Spencer et al., 1951).

A few fatal human cases have been reported which were associated with occupational situations and one case of accidental ingestion resulted in death (reviewed by Browning, 1965).

EDC is a potent mutagen in Drosophila (Shakarnis (1969) cited in Vogel and Chandler, 1974).

Substitution for pesticidal applications such as methyl bromide may be feasible in some cases. However, for certain import and export commodities available substitutes are not acceptable (USDA, 1975).

REFERENCES

Alumot (Olomucki), E. and Z. Harduf (1970)" Impaired Uptake of Labeled Proteins By the Ovarian Follicles of Hens Treated with Ethylene Dibromide", Comp. Biochem. Physiol. 39B, 61-68.

Amir, D. (1973), Sites of Spermicidal Action of Ethylene Dibromide in Bulls", J. Reprod. Fert. 35 (3): 519-525.

Brem, H., Stein, and H.S. Rosenkranz (1974), "The Mutagenicity and DNA-modifying effect of Haloalkanes", Cancer Research, 34, 2576-2579.

Browning, E. (1975), Toxicity and Metabolism of Industrial Solvents, Elsevier, Amsterdam p. 251-252.

Buselmaier, W. et al. (1972)," Critical Considerations on the Host-Mediated Assay, A Method for Detection of Chemically Induced Mutations", Biol. Zentralbl. 91, 311-325.

Castro, C. E. and N. O. Belser (1968),"Biodehalogenation. Reductive Dehalogenation of the Biocides Ethylene Dibromide, 1,2-Dibromo-3-chloropropane, and 2,3 Dibromobutane in Soil", Env. Sci, and Tech, 2 (10), 779-783.

DeSerres, F. and Malling (1970),"Genetic Analysis of the AD-3 Mutants of Neurospora Crassa Induced by Ethylene Dibromide-A Commonly Used Pesticide", Newsletter Env. Mutagen Soc. 3: 36-37.

ENVIRON (1974) Oil and Hazardous Materials Technical Assistance Data Systems File (OHMTADS).

EPA (1975) EDB pesticidal use estimates-Office of Pesticide Programs.

EPA (1975a) Preliminary monitoring data (Sampling and Analysis by MRI) - Office of Toxic Substances, EPA 560/6-75-001.

EPA (1975a) EDB emmission estimates-Mobil Source Air Pollution Control Office.

Esposito, G.G. (1972) Final Report, Analytical Method for Ethylene Dibromide Depletion in Aviation Gasoline U.S. Army, Aberdeen Research and Development Center, Coating and Chemical Laboratory: Aberdeen Proving Ground, Maryland (NTIS-AD 746, 250).

Lloyd, J. W. (July 7, 1975) "Background Information on Ethylene Dibromide", Office of Occupational Health Surveillance and Biometrics, NIOSH.

Malone, B. (1971), "Analytical Methods for the Determination of Fumigants", Residue Reviews 38, p. 24.

McCollister, D. D. R. L. Hollingsworth, F. Oyen, and V. K. Rowe (1956), "Comparative Inhalation Toxicity of Fumigant Mixtures", A.M. A. Arch. Ind. Health 13, 1-7.

McKenry, N.V. (1972), "The Behavior Pesticides containing 1,3-Dichloropropane and 1,2-Dibromoethane in Soils", Diss. Abstr. Int. 34 (7) 3034B, 1974.

McMahon, B. M. (1971)," Analysis of Commercially Fumigated Grains for Residues of Organic Fumigants", JAOAC, 54, 964.

Nachtomi, E., E. Alumot and A. Bondi (1972)," Metabolism of Halogen Containing Fumigants in Mammalians and Birds", Proc. Int. Cong. Pest. Chem., 2nd (1971) vol.6, 495-501.

NCI, (1975) - Personal communication with Dr. C. Cueto.

Olmstead, E. V. (1960)," Pathological Changes in Ethylene Dibromide Poisoning", Arch of Ind. Health, 21, 525-27.

Olson, et al. (1973),"Induction of the Stomach Cancer in Rats and Mice with Halogenated Aliphatic Fumigants", J. Nat. Cancer Inst. 51 (6), 1993-1995.

Rowe, V. K. et al. (1952), "Toxicity of Ethylene Dibromide determined on Experimental Animals", AMA Arch. of Ind. Hyg. and Occup. Med. 6, 158.

Sayers, R.R., W.P. Yant, C.P. Waite, and F. A. Patty (1930) Public Health Reports. Reprint No. 1349.

Schlinke, J. C. (1969) "Toxicological Effects of Five Soil Nematocides in Cattle and Sheep", J. Am. Vet. Med Assoc. 155 (8), 1364-1366.

Shakarnis, V.F., Genetica 5, 89 (1969).

Soulages, N.L. (1966) "Simultaneous Determination of Lead Alkyls and Halide Scavengers in Gasoline by Gas Chromatography with Flame Ionization Detection". Anal. Chem. 38 (1), 28-33.

Soulages, N.L. (1967)" Determination of Methyl Ethyl Lead Alkyls and Halide Scavengers in Gasoline by Gas Chromotography and Flame Ionization Detection", Anal. Chem. 39 (11), 1340-41.

Spencer, H.C., V.K. Rowe, E.M. Adams, D.D. McCollister, and D.D. Irish (1951), A.M.A. Arch. Ind. Hyg. Occupational Med. (4) 482.

SRI- Stanford Research Institute-personal communication.

Tessman, I. (1971), "Induction of Transversions and Transitions by 1,1-dibromoethane", Newsletter Environ. Mutagen Soc. 4: 33.

The Chemical Economics Handbook, Stanford Research Institute, 1975.

The Merck Index, 8th Edition Merck & Co., Inc. 1958.

The U. S. Tariff Commission Reports, 1969-1972.

Vogel, E. and J.L.R.Chandler (1974),"Mutagenicity Testing of Cyclamate and Some Pesticides in Drosophila Melanogaster", Experientia, 30 (6), 621-623.

Von Oettingen, W. F. (1958) "The Halogenated Hydrocarbons: Toxicity and Potential Dangers", Public Health Service Reports No. 414, p.152.

Wit, S. L. A.F.H. Besemer, H.A. Das, W. Goedkoop, F.E. Loosjes, and E.K. Mappelink (1969), "Results of an investigation on the regression of three fumigants (carbon tetrachloride, ethylene dibromide, and ethylene dichloride) in wheat during processing to bread", Report# 36/69 Tox, National Institute of Public Health, Utrecht, The Netherlands.

APPENDIX A

NCI Memorandum of Alert - Ethylene Dibromide

To Schweitzer

TO : Chairman of DHEW Committee to Coordinate Toxicology and Related Programs
Through: Director for DCCP, NCI

DATE: October 16, 1974

FROM : Associate Director for Carcinogenesis, DCCP, NCI

SUBJECT: Memorandum of Alert - Ethylene Dibromide

1. The Director of our Bioassay Operations Segment has informed me of preliminary findings in bioassays in which ethylene dibromide is being tested for carcinogenicity. These preliminary results suggest a strong carcinogenic activity both in rats and in mice. The main tumor response is represented by squamous cell carcinomas of the stomach.

2. Ethylene dibromide is an industrial chemical having significant commercial production. The total capacity in the United States is estimated to be approximately 350,000,000 pounds a year. Its major uses are as a lead scavenger in motor fuels, an agricultural fumigant, a solvent, and an intermediate in the production of dyes and pharmaceuticals.

3. I am bringing this information to your attention since I think it is important that the appropriate agencies be made aware of our concerns with this matter and so that we may give it our attention in advance of the conclusion of the studies and the compilation of a detailed report for publication.

4. It must be emphasized that the information transmitted to you represents only a statement of concern and that no definite conclusions as to the carcinogenicity of the substance may be reached until all of the data from histopathology examinations has been received and evaluated. It is expected that such a final report will be available to you in the near future.

Umberto Saffiotti, M.D.

Enclosure: Memo of 10/4/74

cc:
Dr. Kraybill
Dr. Mehlman
Dr. Page
Dr. Rauscher

TO : Associate Director for Carcinogenesis
DCCP, NCI

DATE: 10/4/74

FROM : Chief, Carcinogen Bioassay and Program
Resources Branch, CG, DCCP, NCI

SUBJECT: Memorandum of Alert - Ethylene Dibromide

1. Preliminary results of the carcinogenesis testing of ethylene dibromide, CAS No. 106-93-4, indicate strong carcinogenic activity in both rats and mice. The predominant tumors are squamous cell carcinomas of the stomach.

2. Ethylene dibromide, synonyms - (a) 1,2-dibromoethane; (b) ethane, 1-2-dibromo-; and (c) ethylene bromide has been tested by gastric intubation in both sexes of Osborne Mendel rats and B6C3F1 mice. Details are presented in the attached information sheet.

3. The results of these studies are being tabulated and analyzed at this time. It is expected that an official report will be available within a few weeks. Additional details will be made available upon request.

Norbert P. Page, D.V.M.

Enclosure

BIOASSAY INFORMATION SHEET

Carcinogen Bioassay and Program Resources Branch
Landow Building, Room C325
National Cancer Institute
Bethesda, Md. 20014

Chemical Ethylene Dibromide CAS No. 106-93-4 CBDS No. C00522

	Rat (Osborne Mendel)		Mouse (B6C3F1)	
	Male	Female	Male	Female
Group Size	50	50	50	50
Route of Administration	ORAL	ORAL	ORAL	ORAL
Dose Levels	80 mg/kg/day 40 mg/kg/day	80 mg/kg/day 40 mg/kg/day	120 mg/kg/day 60 mg/kg/day	120 mg/kg/day 60 mg/kg/day
Frequency of Administration	5 days/wk	5 days/wk	5 days/wk	5 days/wk
Duration of Treatment*	18 mo	18 mo	18 mo	18 mo
Duration of Observation*	6 mo	6 mo	3 mo	3 mo
Total Length of Test*	24 mo	24 mo	21 mo	21 mo
Expected Date of Completion	November 1974	November 1974	November 1974	November 1974

* Planned - studies were terminated early due to early carcinogenic response.

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