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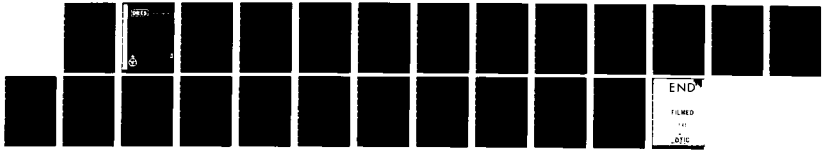

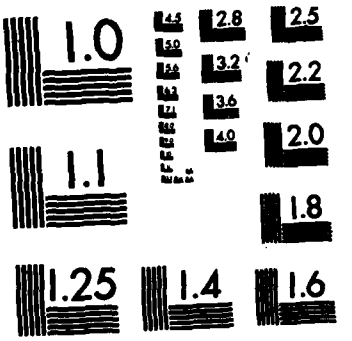

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by

C.E. Mendoza and I.W. Coleman

Project No. 13D10

December 1982

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ABSTRACT

The current toxicology of ethylene oxide is emphasized in this report. Studies such as acute toxicity, subacute toxicity, mutagenicity, reproductive toxicology and carcinogenicity are presented. The overall toxicological implications and a recommendation on the use of ethylene oxide are briefly discussed.

(U)

ACKNOWLEDGEMENT

We would like to acknowledge Dr. T. Lewis and Dr. K. Anger of NTP, NIOSH, Cincinnati, Ohio, U.S.A., and Dr. W. Snelling of Union Carbide Corporation, Bushy Run Research Center, Export, Pennsylavania, U.S.A. for the most recent and unpublished toxicological information. We also acknowledge Capt W.M. Smith, Medical Officer, CFB Suffield, Ralston, Alberta, for his interest and cooperation in the preparation of this report. Likewise, we thank Miss Helena Walsh for typing the manuscript.

This report was prepared in response to the request of Dr. M.C. Hamblin, Director, Defence Sciences Division, DRES, on September 16, 1982.

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SUMMARY

Ethylene oxide is used as a fumigant to sterilize surgical equipment and as a fungicide for agricultural commodities. It is a liquid at below 12°C and has a boiling point of 10.7°C. It is readily soluble in water and most organic solvents.

Its chemical properties make the compound very reactive on mucous membranes and cellular components. Symptoms of acute poisoning are irritation of the skin, mucous membranes and lungs; pulmonary edema; depression of the central nervous system; lacrimation; nausea or vomiting; and convulsion. Severe pulmonary edema could lead to death. Deaths after a few days are due to liver and kidney failure.

Adverse effects were demonstrated by some of the specific, standard toxicological studies such as acute, skin and eye irritation, mutagenicity, reproduction, and oncogenicity tests. Its LD_{50} values of less than 500 mg/kg of body weight rank ethylene oxide among the dangerous poisons. It causes severe skin burns and eye irritation without apparent permanent damage. Moreover, this chemical is highly mutagenic in

SUMMARY (Cont'd)

microbiological and mammalian systems. Reproductive impairment was observed in both male and female test animals that were exposed to ethylene oxide vapour. A single exposure of the male rats to vapour at 1000 ppm for 4 hours resulted in reproduction abnormalities corresponding to the effect on germinal cells after meiotic divison. Recent oncogenicity studies on rats and cynomologus monkeys indicated that ethylene oxide causes leukemia.

It should be noted also that ethylene oxide in the presence of water produces ethylene glycol. Subchronic and chronic exposures to ethylene glycol result in blood clotting abnormalities, reproductive failure as well as tumours in laboratory animals.

Considering the chemical nature, and the serious toxicological effects on the mammalian systems, ethylene oxide should be regarded as a dangerous compound. Therefore, it should be handled and used with utmost care. Monitoring of its residues and by-products must be conducted, particularly when it is used to sterilize equipment that will be used directly on humans. The threshold limit value (TLV) is 1 ppm or 2 mg/m³ of air.

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INTRODUCTION

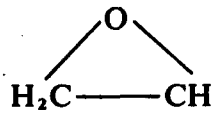
The present report briefly summarizes the toxicological data and clinical symptoms of ethylene oxide poisoning. It also attempts to give the most recent findings regarding the toxicological effects, including oncogenicity, of ethylene oxide. Highlights of the most recently completed but unpublished studies have been obtained through the courtesy of Dr. Trent Lewis (Project Leader for ethylene oxide studies and Contact Person for Pulmonary Toxicology, National Institute of Occupational Safety and Health (NIOSH), National Toxicology Program, Public Health Service, U.S. Department of Health and Human Services, Cincinnati, Ohio, U.S.A.).

The topics discussed in this report are chemistry, uses, symptomatology, and toxicological studies including skin and eye irritation, mutagenicity, reproduction, teratogenicity, oncogenicity, acute and subacute toxicity. Toxicological information on ethylene glycol, the product of ethylene oxide hydrolysis, is included in order to give a balanced perspective of the hazards due to the use of ethylene oxide.

CHEMICAL NAME

Ethylene oxide, 1,2-epoxy ethane, oxidoethane, oxinane.

STRUCTURE



C_2H_4O

MOLECULAR WEIGHT

44.06

PROPERTIES

Colourless flammable gas at ordinary temperature and pressure; liquid below 12°C, boiling point 10.7°C; freezing point −111°C, specific gravity (at 0°C/4°C water) 0.891, (at 20°C/4°C water) 0.8694, (at 60°C/4°C water) 0.804; refraction index (for 20°C and sodium light) 1.3597. Soluble in water, alcohol, ether (Merck Index, 9th ed., 1976).

Inflammable at concentrations greater than 3% in air (Spencer, 1982).

USES

As a fumigant for food stuffs and textiles; to sterilize surgical instruments; as an agricultural fungicide. In syntheses, especially in the production of ethylene glycol. In manufacture of acrylonitrile and nonionic surfactants (Merck Index, 9th ed., 1976).

SYMPTOMATOLOGY

Intense irritation of skin (blisters), mucous membranes, and lungs, with production of pulmonary edema. Irritation and pain usually act as adequate warnings but **not always**. Prompt deaths are thought to be the result of central depression with respiratory arrest; in delayed deaths for several hours, deaths are due to pulmonary edema; those after a few days are due to liver and kidney damage (Gosselin *et al.*, 1976). Lacrimation, nausea or vomiting, convulsion, hyperactivity of the gastro-intestinal system are observed in human exposures (Lewis and Tatken, 1982).

TOXICOLOGICAL DATA

I. Skin and eye irritation data

A. Lewis and Tatken, 1982:

— Human skin — 1%/7 seconds exposure, no results given.

— Rabbit eye — 18 mg/6 hours exposure, moderate irritation.

B. Grant, 1974:

— Rabbit eye — a drop of ethylene oxide caused intense conjunctivitis but cleared in 4 days.

II. Mutation data

A. Lewis and Tatken, 1982:

— *Salmonella typhimurium* — 40 μmol/plate.

— *Escherichia coli* — 3500 μmol/10 hours.

— *Neurospora crassa* — 140 mmol/L/10 minutes.

— *Drosophila melanogaster*, cytogenetic analysis, (parenteral) — 55 mmol/L.

— *D. melanogaster*, sex chromosome loss and nondisjunction, (parenteral) — 5 mmol/L.

— Human fibroblast, sister chromatid exchange — 36 ppm/24 hours.

— Rat bone marrow, cytogenetic analysis, (*in vitro*) — 30 μg/L/2 days.

— Rat, cytogenetic analysis (inhalation) — 1 μg/L for 17 weeks.

— Rat, cytogenetic analysis (p.o.) — 9 mg/kg.

*— Rat, micronucleus test on "lymphocytes?" (i.v.) — 200 mg/kg.

**— Rat dominant lethal test (inhalation) — 1000 ppp/4 hours.

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* Mammalian, *in vivo*, studies; perhaps "lymphocytes?", since they are commonly used in this type of test.

** Most relevant mammalian, *in vivo*, study to acute exposure of humans to ethylene oxide (see also Embree *et al.*, 1977).

*— Mouse micronucleus test on "lymphocytes?" (i.p.) — 150 mg/kg.

*— Mouse micronucleus test on "lymphocytes?" (i.v.) — 200 mg/kg.

— Mouse unscheduled DNA synthesis test on "skin fibroblast or primary hepatocytes" (inhalation) — 300 ppm.

— Mouse dominant lethal test (inhalation) — 500 ppm for 80 hours, intermittent dosing.

— Mouse dominant lethal test (i.p.) — 150 mg/kg.

— Mouse lymphocyte or mammalian somatic cell mutation (*in vitro*) — 5 μmol/L.

— Mouse fibroblast heritable translocation test (i.p.) — 30 mg/kg for 25 days, intermittent dosing.

B. Embree *et al.*, 1977:

— Dominant lethal study on male Long-Evans rats exposed once to 1000 ppm of ethylene oxide for 4 hours, mated each week to groups of 2 females for 10 weeks, using trimethlylenemelamine as the positive control.

— Results:

a) Significant increase in post-implantation foetal deaths.

b) Significant increase during the first 5 weeks of the experiment, corresponding to residence time of germinal cells exposed to ethylene oxide after their meiotic division (cell division that results in the formation of gametes).

III. Reproduction effects data

A. Lewis and Tatken, 1982:

— Foetotoxicity in rat (inhalation), lowest effect dose or concentration (LDLo) 100 ppm, 6 hours per day at 6 – 15 days of pregnancy.

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* Mammalian, *in vivo*, studies; perhaps "lymphocytes?", since they are commonly used in this type of test.

- Live birth litter size — rat (inhalation), LDLo 100 ppm, 6 hours per day; males treated for 60 days premating, 1 – 19 days of pregnancy.
- Testes, sperm ducts, epididymis; pre-implantation mortality, LDLo 3600 $\mu g/m^3$ for 24 hours per day; males treated for 60 days premating.
- Post implantation mortality in mouse (i.v.), LDLo 225 mg/kg at 10 – 12 days of pregnancy.
- Musculo-skeletal system in mouse (i.v.), LDLo 450 mg/kg at 8 – 10 days of pregnancy.
- Before birth ("caesarian section") litter size; foetotoxicity in mouse (i.v.), LDLo 450 mg/kg at 10 – 12 days of pregnancy.

B. Snelling, *et al.*, 1982a:

- Male and female Fischer rats were exposed to ethylene oxide vapour for 6 hours per day, 5 days per week for 12 weeks. Animals were mated and the females were continued on exposure from Day 0 through Day 19 of gestation for 6 hours per day, 7 days per week.
- Results:
  a) The major treatment-related adverse effect was significantly fewer pups born per litter in the highest exposure level only.
  b) There were fewer implantation sites per pregnant female, and a smaller ratio of the number of foetuses born to the number of implantation sites per pregnant female in the highest level group than in any other groups.
  c) The gestation period was significantly longer in the 100-ppm group than in the control group.
  d) Fertility indices for the treated males and females were not statistically different from the control group.
  e) No significant adverse effects were observed in terms of body weight gain, survival and other toxic signs in the F_0 and F_1 generations.

C. National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA), Jefferson, Arkansas study (under the direction of Dr. Carole Kimmel), personal communciation September 20, 1982 with Dr. T. Lewis, NTP:

- No detail protocol or schedule of the study was obtained.
- Teratogenicity study on rabbits exposed to ethylene oxide.
- Results:
  - Increased incidence of foetotoxicity, no teratogenicity observed.

IV. Oncogenic data

A. Lewis and Tatken, 1982:

- Neoplasma (benign or lacking complete description) in mouse (s.c.), LDLo 1090 mg/kg for 91 weeks, intermittent dosing.
- Currently being tested for the National Toxicology Program (NTP), Public Health Service, U.S. Department of Health and Human Services, by Battelle Northwest Laboratory.

B. Personal communication, September 20, 1982, with Dr. Trent Lewis, National Toxicology Program (NTP), NIOSH, Department Health and Human Services, Cincinnati, Ohio:

1. NTP, NIOSH (being conducted by Battelle Northwest Lab., monitored by Tracor-Jitco for NTP under the direction of Dr. T. Lewis).
   - Chronic inhalation study on mice, male and female, exposed to 0, 50, or 100 ppm of ethylene oxide for 6 hours per day, 5 days per week for 2 years.
   - The study was started in late August, 1981, is in progress as of September 20, 1982. There is no progress report available.
2. NIOSH study (terminated in 1981, final report in preparation)

— Chronic inhalation study on Fischer 344 rats, females only, exposed to 0, 50, or 100 ppm of ethylene oxide for 6 – 7 hours (or approximately 6.8 hours) per day, 5 days per week for 2 years.

— Results:

— Increased incidence of leukemia that is treatment-related.

3. NIOSH study (terminated in 1981, final report in preparation)

— Chronic inhalation study on Macaca fascicularis (cynomologus monkey), males only, exposed to 0, 50 or 100 ppm of ethylene oxide for 6 – 7 hours per day, 5 days per week for 2 years.

— Results:

a) Treatment-related increase in chromosomal abberation and sister chromatid exchange in the circulating lymphocytes.

b) Treatment-related significant decrease in sperm motility and counts.

c) Histopathological abnormality of the nucleus gracilis of the dorsal column, central nervous system, related to tactile sensory; also increased axonal bodies. Histopathology was conducted by Dr. H. Spring, Midwest Research Institute and Kansas University, Kansas City, Missouri (Project Officer for histopathological and behavioural studies, Dr. Kent Angers of NIOSH at Cincinnati, Ohio, personal communication, September 21, 1982).

C. Snelling *et al.*, 1982b:

— Chronic inhalation study on Fischer 344 rats, male and

female, exposed to 0, 10, 33, or 150 ppm of ethylene oxide for 6 hours per day, 5 days per week for 2 years.

— Results:

a) Depression of body weight and increase in mortality at the 33 and 150 ppm levels.

b) No consistent pattern of association of histologically confirmed organ damage with any alteration in urinalysis, hematology, serum clinical chemistry, or organ weights.

c) Skeletal muscle atrophy in both sexes at 150 ppm at 24 months.

d) Increased prevalence of mononuclear leukemia, treatment-related in females at the 10, 33 or 150 ppm level.

e) Increased incidence of more than two neoplasms per rat in the three treatment groups.

f) Increased incidence of malignant neoplasm in females at the 33 or 150 ppm level.

g) Treatment-related increase in peritoneal mesothelioma in the male rats at the 33 or 150 ppm level.

h) Incidence of mononuclear leukemia and peritoneal mesothelioma in the control group comparable to historical published background.

i) The possible contribution of sialodacryoadenitis viral outbreak (which occurred during the 15th exposure month) to the ethylene dioxide exposure related tumors is unknown.

D. Reyniers *et al.*, 1964:

— Male and female mice (ALBM-2, colony 101-F) were exposed to the corncob bedding sterilized with ethylene oxide

up to 900 days. They were observed for blood dyscrasia, reproductive capacity and tumour incidence.

— Mice that were accidentally exposed to the ethylene oxide-treated bedding prior to the intentional exposure experiment mentioned in the preceding paragraph were observed for reproductive failure.

— Results:

a) Female mice exposed to corncob bedding treated with ethylene oxide experienced reproductive failure.

b) Survivors (90%), 400 to 900 days old mice, developed tumours of various kinds and in various sites.

c) Graafian follicles and corpora lutea rarely found; abnormal ovaries in almost all animals.

d) No tumours in either males or females up to 600 days old that were exposed to non-treated corncob bedding.

e) Males exposed for less than 50 days to the toxic bedding lived longer, had markedly lengthened blood-clotting time, and died of hemorrhage.

f) Only one female showed extensive hemorrhages.

g) Attempts to breed surviving males failed.

V. Toxicity data

A. Lewis and Tatken, 1982:

— Convulsion, nausea or vomiting, changes in lungs, thorax or respiration in adult woman (inhalation), LDLo 500 ppm for 2 minutes.

— Lacrimation, changes in structure and function of salivary glands, hypermotility of the gastro-intestinal tracts, diarrhea in rat (inhalation), LDLo 72 mg/kg; in dog (inhalation), LC_{50} = 960 ppm for 4 hours exposure.

— Irritation in human (inhalation), LDLo 12500 ppm for 10 seconds.

— Rat (p.o.) LD_{50} = 72 mg/kg.

— Mouse (inhalation) LD_{50} = 836 ppm for 4 hours.

— Mouse (i.p.), LDLo 100 mg/kg.

— Mouse (i.v.), LD_{50} = 290 mg/kg.

— Rabbit (i.v.), LDLo 175 mg/kg.

— Guinea pig (p.o.), LD_{50} = 270 mg/kg.

— Guinea pig (inhalation), LDLo 7000 ppm for 150 minutes (2.5 hours).

*— Rat (inhalation), LD_{50} = 1462 ppm for 4 hours.

*— Rat (p.o.), LD_{50} = 330 mg/kg.

B. Allan *et al.*, 1962:

— Blood clotting study on mice, male and female, exposed to either pine shavings (bedding), sterilized with ethylene oxide, for 6 months; by gavage administration of 0.25 mg or 2.5 mg of ethylene oxide in olive oil per day for 4 weeks; or by i.v. administration of 2.5 μg or 2.5 μg of ethelene oxide in saline solution per day for 4 weeks. An untreated control group was also observed.

— Ethylene glycol ($HOCH_2CH_2OH$) was also administered to the mice at 10^{-2}, 10^{-3}, and 10^{-4} dilutions by gavage each weekday (interpreted as 5 days/week) for 12 weeks.

— Extracts of the control shavings, or the shavings sterilized with ethylene oxide, were also administered to the mice at 10^{-1}, 10^{-2}, and 10^{-3} dilutions.

— Results:

a) Unautoclaved ethylene oxide administered by gavage (0.25 mg or 2.5 mg/day) or i.v. (2.5 μg or 25 μg/day) produced no clotting abnormality in the mice.

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* Data from Sax, 1979.

b) Haemothorax, bleedings at various body sites, jaundice and subsequent deaths observed on males only reared in bedding sterilized with ethylene oxide.

c) Both ethylene glycol and extracts of shavings that had been autoclaved with ethylene oxide produced increased specific clotting abnormalities, which appeared predominantly in male mice.

d) Autoclaved ethylene oxide in the presence of water produced ethylene glycol, which is responsible in the production of blood clotting abnormalities.

e) Ethylene glycol administered by gavage at 1:5 to 1:10 dilutions produced the same blood clotting abnormalities in mice.

VI. Threshold limit value — time weighted average or TLV-TWA (Amer. Confer. Gov. Ind. Hyg., 1982)

— Intended changes for 1982, 1 ppm or 2 mg/m³ air, with a warning that it may be a carcinogen.

GENERAL COMMENTS

Mackel (1974) of the Public Health Service, U.S. Department of Health, Education and Welfare (now Department of Health and Human Services) recommended that ethylene oxide gas autoclaving be used on all non-steamable-autoclavable reuseable equipment. It was recommended that biological sterility controls be used during the sterilization operation and that all materials must be adequately aerated before use. The use of a heated aerator which circulates and continuously vents air at 50 to 60°C for 8 to 12 hours.

In 1977, the National Institute for Occupational Safety and Health (NIOSH) issued a special occupational hazard review and recommendations for the use of ethylene oxide as a sterilant in medical facilities (Glaser, 1977). The report includes reviews of effects of ethylene oxide in animals, lower biological systems and humans. Haemolysis has been reported with ethylene oxide sterilized devices used for blood perfusion, and with devices used for i.v. administration in patients. Subsequent studies in dogs treated with ethylene oxide gave conflicting results. Perhaps these conflicting results were obtained since haemolysis may be more associated with ethylene glycol than ethylene oxide, the test material used. Ethylene glycol has been implicated with internal haemorrhages and other blood dyscrasia in experimental animals (Allen *et al.*, 1962; Reyniers *et al.*, 1964).

Leukemia observed in mice, rats and monkeys parallels that observed in three industrial workers exposed to ethylene oxide for a long period of time (Hogstedt *et al.*, 1979). It should be emphasized that leukemia was observed after a prolonged chronic exposure. However, with a single or short experimental exposure, it should be noted that the test animals were not observed long enough for the development of leukemia or other diseases with long latent period.

CONCLUSION

The reports reviewed indicated that ethylene oxide is highly mutagenic in animals, in microbial systems, and in isolated animals and humans cells. Reproductive failures in both male and female test animals exposed to ethylene oxide were also observed. Recently completed and unpublished chronic toxicity studies indicated that it causes leukemia in rodents and cynomologus monkeys.

Since ethylene oxide reacts with water to produce ethylene glycol, particularly under heat and pressure, secondary hazard due to ethylene glycol can be expected. Ethylene glycol causes internal haemorrhages and other blood dyscrasia in the laboratory animals. It is a very stable compound, with a boiling point of 197.6°C at 760 mm Hg pressure to 20°C at 0.06 mm Hg pressure. Evacuation of ethylene glycol will be very difficult particularly from charcoal-containing cannisters.

We recommend, therefore, that ethylene oxide should not be used to sterilize equipment such as cannisters, particularly if they contain adsorbents. Adequate venting of enclosed cannisters and adsorbed gas may not be achieved unless specially tested procedures are followed. In addition, the hydrolysis product, ethylene glycol, has a very low vapour pressure which makes it difficult to be completely evacuated from the cannisters containing absorbents.

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13. ABSTRACT

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Acute Toxicity
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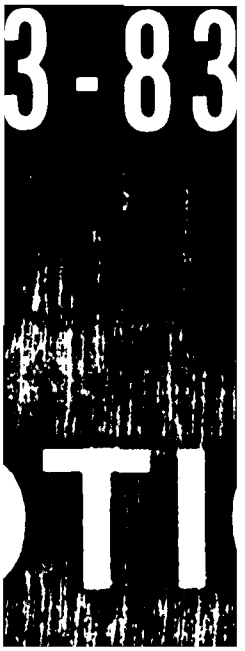
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