

U.S. Army Center for Health Promotion
and Preventive Medicine

**Wildlife Toxicity Assessment for
Ethylene**

JANUARY 2006

**Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program**

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**FINAL REPORT
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Department of the Army
U.S. Army Center for Health Promotion and Preventive Medicine

Wildlife Toxicity Assessment for Ethylene

CAS No. 74-85-1

January 2006

1. Introduction

Ethylene is a colorless gas that is produced by the petrochemical industry in vast quantities throughout the world. As summarized by the International Agency for Research on Cancer (IARC), the compound serves as the "building block" for the production of polyethylene, as well as other important chemicals and intermediates such as ethylene oxide, ethylene dichloride, ethylbenzene, ethylene glycol, ethanol and vinyl acetate monomer among others (IARC 1994). In medicine, the compound has been used as an anaesthetic when mixed with air. However, the use of this formulation has been largely discontinued because of the explosive nature of the ethylene-oxygen mixture. The compound is released to the environment as a product of burning vegetation, a by-product of petroleum refining, through production by steam cracking of hydrocarbon feedstocks, incomplete combustion of fossil fuels, in automobile and diesel exhausts and by sewage treatment plants (HSDB 2001). Ethylene is also produced and emitted by all plants and hence is present naturally in the environment. Human beings and other mammals also produce the compound endogenously.

This Wildlife Toxicity Assessment summarizes current knowledge of the toxicological impacts of ethylene on wildlife. Evaluating the toxicity of ethylene is intended to contribute to the derivation of toxicity reference values (TRVs) that could serve as screening-level benchmarks for wildlife in the vicinity of contaminated sites. The protocol for the performance of this assessment is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. Toxicity Profile

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were electronically searched April 20, 2001 and May 2, 2001, using Dialog to identify primary reports of studies and reviews on the toxicology of ethylene. Separate searches were carried out linking the compound to mammals, birds, and reptiles and amphibians (combined). In general, a two-tiered approach was used in which all citations were first evaluated as titles and "key words in context." All available abstracts of those articles that were selected

in the first tier as possibly relevant to TRV development were then evaluated for relevancy and retention for evaluation in the second tier. For ethylene, 9 articles were marked for retrieval from 538 initial hits, a disparity arising because the initial sweep captured a substantial number of reports of studies that featured the use of "ethylene" as part of the name of a large number of other compounds. These were eliminated in Tier 2 of the selection process. Details of the search strategies and the results of each are documented in Appendix A.

In addition to Dialog searching, a number of U.S. Army reports were identified in the Defense Technical Information Center (DTIC). Secondary references and sources of information on ethylene included the National Library of Medicine's Hazardous Substances Databank (HSDB 2001) and IARC monographs (IARC 1979, 1994).

2.2 Environmental Fate and Transport

Ethylene is a ubiquitous component of the atmosphere, with concentrations reaching $5 \mu\text{g}/\text{m}^3$ at remote sites. However, its concentration can range greater than $1000 \mu\text{g}/\text{m}^3$ in urban centers, largely as a result of vehicle exhaust emissions. Ethylene is produced for a variety of uses in large quantities; about 47 billion pounds were produced in 1995 (Chemical and Engineering News 1996). Industrial release of ethylene to the air is substantial throughout the developed world. IARC (1994) reports an estimated total industrial release of 17,400 tons of ethylene in the United States in 1991. A report from the American Petroleum Institute (Suriano 2003) in support of the EPA Toxic Release Inventory indicates that 1.7 billion pounds of ethylene was released by petroleum refineries in 2000.

Volatilization of soil-borne ethylene is likely, based on the compound's high vapor pressure of 5.2×10^4 and a Henry's Law constant of $2.3 \times 10^{-1} \text{ atm}\cdot\text{m}^3/\text{mole}$ at 25°C (HSDB 2001). As listed in Table 1, these and other physical-chemical characteristics also favor volatilization of ethylene from the surface of marine and freshwater systems. However, although sparingly soluble in water, the compound has been detected in oceans, lakes, and rivers in and around the United States. For example, concentrations of ethylene up to 35 nL/L were measured in water samples taken in the Mississippi delta.

Table 1. Summary of Physical-Chemical Properties of Ethylene

CAS No.	74-85-1
Molecular weight	28.05
Color	Colorless

Table 1. Summary of Physical-Chemical Properties of Ethylene

Physical state	Gas
Melting point	-169°C
Boiling point	-103.7°C
Odor	Sweet
Solubility	131 mg/L in water at 20-25 °C slightly soluble in benzene, ethanol, acetone, soluble in diethyl ether
Partition coefficients:	
Log K _{ow}	1.13
Log K _{oc}	2.0–2.5
Vapor pressure at 25 °C	5.2×10^4 mm Hg
Vapor Density	0.978 (air = 1)
Henry's Law constant at 25 °C	2.3×10^{-1} atm.m ³ /mole
Conversion factors	1 ppm = 1.15 mg/m ³ 1 mg/m ³ = 0.87 ppm

Sources: HSDB (2001), IARC (1994)

A number of mechanisms have been suggested for how the chemical is degraded in the environment. For example, the compound can degrade rapidly in the atmosphere as it reacts with photochemically-produced hydroxyl radicals. This process has a half-life of about 1.9 days. Nitrate radicals and ozone will also cause ethylene degradation, however at a lower rate. Ethylene can also be broken down as a result of microbial action as determined by pure culture research, however, it is expected to oxidize to ethylene oxide which is not metabolized further and may accumulate in the environment (HSDB 2001).

Given the volatility of ethylene, it is unlikely that it would persist in the environment long enough to allow for significant exposures to terrestrial wildlife. In the event that exposure would occur, the most likely route would be inhalation followed possibly by the dermal route. Importantly, ethylene is readily converted to ethylene oxide, which is somewhat more stable and could pose some risk to wildlife.

2.3 Summary of Mammalian Toxicity

2.3.1 Mammalian Toxicity - Oral

Given the gaseous nature of ethylene at ambient temperatures and pressures, there are no data on the toxicological effects of ethylene when administered via the oral route.

2.3.1.1 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

Not applicable.

2.3.2 Mammalian Inhalation Toxicity

2.3.2.1 Mammalian Inhalation Toxicity – Acute

Due to the fact that ethylene serves as a rapid onset anesthetic, humans and animals have been exposed to relatively high concentrations without notable long-term adverse effects. For example, rats exposed to ethylene at concentrations of up to 500,000 ppm for 5 hours are reported to have suffered no long-term adverse effects (HSDB 2001). The apparent tolerance to high concentrations of ethylene in animals and humans has precluded the identification of a reliable compound-specific median lethal concentration (LC₅₀). However, it appears that concentrations of ethylene necessary to induce effective anesthesia come close to inducing hypoxia as the proportion of oxygen in the ethylene-air mixture is reduced.

Although there are few if any toxicological consequences of exposure to ethylene via inhalation, the ability of the compound to react with biological macromolecules has been demonstrated. For example, Eide et al. (1995) exposed male Sprague-Dawley rats to ethylene (one of a range of alkenes under investigation) at 300 ppm for 12 hours/day on three separate days. Exposure took place in a conically-shaped steel chamber with a glass door and walls. At termination, aliquots of blood and samples of lung, brain, liver, kidney, and peripheral fat were measured for ethylene. The formation of DNA adducts in liver and lymphocytes were monitored using the ³²P-postlabelling technique detected using gas chromatography/mass spectrometry. N-(2-hydroxyalkyl) valine adducts of hemoglobin and 7-alkylguanine adducts of DNA were detected consistently in these experiments, including N-(2-hydroxyethyl) valine and 7-ethylguanine when ethylene was used as the test compound.

2.3.2.2 Mammalian Inhalation Toxicity – Subchronic

An experiment by Vergnes and Pritts (1994) used a subacute dosing regime to examine ethylene's ability to induce the formation of micronuclei in the bone marrow of male F344 rats and B6C3F1 mice. Ten animals/group were exposed to 0, 40, 1000, and 3000 ppm ethylene, 6 hours/day, 5 days/week for 4 weeks, with bone marrow collected 24 hours after the last exposure. Exposure took place in a steel inhalation chamber with glass windows. Examination of cell smears revealed little if any formation of micronuclei or polychromatic nuclei in ethylene-exposed groups, although the incidence of these features was significantly increased in the cells of animals receiving 200 ppm ethylene oxide, a major carcinogenic metabolite of ethylene. This finding appears uncharacteristic in view of the likelihood that ethylene oxide is a metabolite of ethylene. However, the contradiction may have been explained by Walker et al. (2000) who used a similar experimental protocol to show that while both ethylene and ethylene oxide induce the formation of N-(2-hydroxyethyl) valine in hemoglobin and N7-(2-hydroxyethyl)guanine in DNA, only ethylene oxide had the ability to increase the frequency of

Hprt mutants in splenic T cells. The authors presented evidence to show that the cytochrome P4502E1-mediated conversion of ethylene to ethylene oxide saturates at levels that are insufficient to trigger the toxic responses that are typical of ethylene oxide exposure.

The Chemical Industry Institute of Toxicology (CIIT) has carried out two full-scale studies on the toxicology of ethylene, one of which was reported by Rhudy et al. (1978). The protocol featured the exposure of 15 "albino" rats/sex/group to 0, 300, 1000, 3000, or 10,000 ppm ethylene, 6 hours/day, 5 days/week for 13 weeks. Ethylene was delivered in unspecified inhalation chambers. During the study clinical signs, mortality, body weights, and food consumption were monitored daily; clinical chemistry, hematological, and urinalysis parameters were monitored in controls and high dose groups on days 6, 45 and 83; and full necropsies and histopathological evaluations were carried out on all survivors at termination. However, there were no compound-related differences in treatment groups compared to controls in any of the parameters under evaluation.

2.3.3.4 Mammalian Inhalation Toxicity – Chronic

The second CIIT study extended the duration to 24 months for 120 F344 rats/sex/group exposed to 0, 300, 1000, or 3000 ppm ethylene (Hamm et al. 1984). Exposure took place in four glass and stainless-steel chambers. Animals were euthanized on an interim basis after 6, 12, and 18 months, with these subjects and all survivors monitored for survival, clinical signs, ophthalmologic characteristics, hematology, clinical chemistry, and urinalysis. A full suite of histopathological examinations were carried out in control and high dose groups although, in these as in all other parameters under investigation, there appears to have been no compound-related effects.

2.3.3.5 Studies Relevant for Mammalian TRV Development for Inhalation Exposures

The use of high concentrations of ethylene as an anesthetic, with full recovery of faculties on cessation of exposure, is consistent with the negative toxicological results outlined in Sections 2.3.3.1–2.3.3.4. Taken together, these findings point to the benign nature of the compound in biological systems and argue against the likelihood that a viable TRV for ethylene can emerge from the overall toxicological information on the compound. However, the formation of 2-hydroxyethyl derivatives of hemoglobin and guanine shows that ethylene has biochemical activity, most likely mediated through its ethylene oxide intermediate. The disparity between the benign effects of ethylene and the more severe effects of ethylene oxide in toxicological tests has been addressed by Walker et al. (2000) and in a review by Bolt (1998) who estimated that exposure concentrations of 1000 ppm ethylene would be equivalent to about 7.5 ppm ethylene oxide. By implication, this concentration would probably be below the threshold at which any toxicological impacts (of ethylene oxide) would become apparent.

2.3.4 Mammalian Inhalation Toxicity – Other

Aveyard and Collins (1997) used Organization for Economic Cooperation and Development (OECD) guideline 421 to test the effects of ethylene on fertility, pregnancy, maternal and suckling behavior, and F1 growth and development in rats (strain unstated) exposed to ethylene. They reported that 10 parental animals/group were exposed head only to 0, 200, 1000, or 5000 ppm ethylene, 6 hours/day from 2 weeks prior to mating until gestation day (GD) 20 (males) or day 4 post-partum (females). No animals died during treatment, and no compound-related effects were evident on weight gain, food consumption, fertility, fecundity, litter characteristics, or on pathology or histopathology in either generation.

2.3.5 Mammalian Dermal Toxicity

No data are available.

2.4 Summary of Avian Toxicology

No toxicological data for the effects of ethylene on avian species was located. Ecotoxicological research on the effects of this compound on birds is recommended.

2.5 Amphibian Toxicology

No toxicological data for the effects of ethylene on amphibian species was located. Ecotoxicological research on the effects of this compound on amphibians is recommended.

2.6 Reptilian Toxicology

No toxicological data for the effects of ethylene on reptiles was located. Ecotoxicological research on the effects of this compound on reptiles is recommended.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

At this time it is not possible to derive a TRV for oral route of exposure for ethylene due to the lack of toxicity data and the gaseous nature of the compound which renders an oral exposure unlikely.

3.1.2 TRVs for Inhalation Exposures for the Class Mammalia

With the use of ethylene in high concentrations as an anesthetic, there is no evidence of toxicological effects occurring at levels that would be likely in the environment. It is, however, evident

that there are toxicological effects through its ethylene oxide intermediate. However, the effects were molecular in nature and were not linked to more toxicologically relevant endpoints such as tumor formation, morbidity or death. As a result, a TRV could not be derived for ethylene at this time.

4. IMPORTANT RESEARCH NEEDS

The limited availability of data on the toxicity of ethylene to wildlife species precludes the development of a TRV. Hence, more studies of the compound and its derivatives are recommended. The toxicity and biochemical activity of ethylene and ethylene oxide warrant attention to explain the relationship between these compounds. Also, chronic toxicity studies on non-mammalian wildlife such as birds, reptiles and amphibians are particularly warranted.

5. References

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APPENDIX A

LITERATURE REVIEW

Separate searches in DIALOG (three in all) were carried out on ethylene on April 20, 2001, and on May 2, 2001.

In the first search the following files were scanned:

File 155 MEDLINE, File 156 TOXLINE, File 5 BIOSIS, File 10 AGRICOLA, File 203 AGRIS, File 399 Chemical Abstracts, File 77 Conference Papers Index, File 35 Dissertation Abstracts, File 40 ENVIRONMENTAL, File 68 Environmental Bibliography, File 76 Life Sciences Collection, File 41 Pollution Abstracts, File 185 Zoological Record, File 6 NTIS, File 50 CAB, File 144 PASCAL, File 34 SCISEARCH, and File 434 SCISEARCH.

The search strategy for **Amphibians & Reptiles**:

- ◆ Chemical name, CAS numbers
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT glycol
- ◆ RD (reduce duplicates)
- ◆ NOT dibromide
- ◆ NOT dichloride
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)

The search strategy for **Birds**:

- ◆ Chemical name, CAS numbers
- ◆ AND chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus()domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))

- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumor? or inhalation or carcin? or cancer?)
- ◆ RD (reduce duplicates)
- ◆ NOT dibromide or dichloride
- ◆ NOT dibromide
- ◆ NOT dichloride

The search strategy for **Laboratory Mammals:**

- ◆ Chemical name, CAS numbers
- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumor? or inhalation or carcin? or cancer?)/ti,de
- ◆ NOT (meeting()poster)
- ◆ NOT (meeting()abstract)
- ◆ NOT (conference()proceeding?)
- ◆ RD (reduce duplicates)
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)
- ◆ NOT (glycols or polymer or poly or tetraacetic or tetraacetate or dichlorides)
- ◆ NOT EDTA
- ◆ NOT (dimethanesulphonate? or dimethanesulfonate? or diamine? or EDS)
- ◆ AND LA=English

The search strategy for **Wild Mammals:**

- ◆ Chemical name, CAS numbers
- ◆ And (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae) or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or

mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or mycogastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?

- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)/ti,de
- ◆ NOT (meeting()poster?)
- ◆ NOT (meeting()abstract?)
- ◆ NOT (conference()proceedings?)
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women? or men? or occupational?)
- ◆ RD (reduce duplicates)
- ◆ NOT steriliz?
- ◆ NOT oxide

When the search retrieved an appreciable number of hits, *keywords in context* were reviewed to minimize costs before any abstracts were downloaded (Tier 1). However, when only a limited number of studies were identified by the search, the abstracts were downloaded at the time of the search (Tier 2).

The second search examined the same files as the first but used the following structure:

For Laboratory Animals

- ◆ CAS Number
- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)

The third search examined the following databases

File 155 Medline, File 156 Toxline, File 535 Thomas Register Online, File 76 Life Sciences Collection, File 185 Zoological Record Online, File 5 Biosis Reviews.

For Birds

- ◆ CAS Number
- ◆ AND (chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus()domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl))
- ◆ RD (Reduce Duplicates)

For **Wild Mammals**

- ◆ CAS Number
- ◆ AND (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae) or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or myocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?)
- ◆ RD (Reduce Duplicates)

For **Amphibians/Reptiles**

- ◆ CAS. Number
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ RD (reduce duplicates)

As noted in Section 2.1, 538 hits on ethylene were obtained in the initial searches, of which 9 were selected for retrieval.