IRIS Summary for the Inhalation Carcinogenicity Assessment of Ethylene Oxide

July 2011

This document is a Final Agency Review/Interagency Science Discussion draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for review of its technical accuracy and science policy implications.

Substance code
Ethylene Oxide; CASRN 75-21-8;

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR Ethylene Oxide

File First On-Line__/__/__

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	not available	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	not available	00/00/0000
Carcinogenicity Assessment (II.)	online	00/00/0000

_I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name – Ethylene Oxide
CASRN -- 75-21-8
Section I.A. Last Revised -- 00/00/0000

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a

daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgr-d.htm for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.A.1. CHRONIC ORAL RfD SUMMARY

NOT AVAILABLE. Noncancer health effects have not been evaluated (U.S. EPA, 2011).

__I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name – Ethylene Oxide
CASRN -- 75-21-8
Section I.B. Last Revised -- 00/00/0000

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers both toxic effects of the respiratory system (portal-of-entry effects) and effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.B.1. CHRONIC INHALATION RfC SUMMARY

NOT AVAILABLE. Noncancer health effects have not been evaluated (U.S. EPA, 2011).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name - Ethylene Oxide
CASRN -- 75-21-8
Section II. Last Revised -- 00/00/0000

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per μg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), ethylene oxide (EtO) is "carcinogenic to humans." In general, the descriptor "carcinogenic to humans" is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer. This descriptor is also appropriate when there is a lesser weight of epidemiologic evidence that is strengthened by specific lines of evidence set forth in the *Guidelines*, which are satisfied for EtO and include the following: (1) there is evidence, although less than conclusive, of cancer in humans associated with EtO exposure via inhalation—strong evidence for lymphohematopoietic cancers and some evidence for breast cancer in EtO-exposed workers; (2) there is extensive evidence of EtO-induced carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure; (3) EtO is a direct-acting alkylating agent

whose mutagenic and genotoxic capabilities have been well established in a variety of experimental systems, and a mutagenic mode of carcinogenic action has been identified in animals involving the key precursor events of DNA adduct formation and subsequent DNA damage, including point mutations and chromosomal effects; and (4) there is strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage, such as chromosomal aberrations, SCEs, and micronuclei in EtO-exposed workers.

___II.A.2. HUMAN CARCINOGENICITY DATA

There is strong, but not conclusive, evidence from epidemiologic studies that EtO is causally associated with lymphohematopoietic cancers in exposed workers. There is also some evidence that EtO may cause an increased risk of breast cancer in female workers. The relevant epidemiologic studies are discussed briefly below. For more details, see the Carcinogenicity Assessment for EtO (U.S. EPA, 2011, Section 3.1 and Appendix A).

The strongest evidence for an association between EtO and cancer is from some high-quality studies of a large National Institute for Occupational Safety and Health (NIOSH) cohort. The NIOSH cohort consists of 18,254 workers (45% male and 55% female) in 14 plants where EtO was used for sterilizing medical supplies, treating spices or in the manufacture and testing of medical sterilizers. Individual exposure estimates were derived for workers from 13 of the 14 plants. Exposures to other chemicals in the workplace were believed to be minimal or nonexistent. The procedures for selecting the facilities and defining the cohort are described in Steenland et al. (1991), and the exposure model and verification procedures are described in Greife et al. (1988) and Hornung et al. (1994). Results of the original mortality study are presented in Steenland et al. (1991) and Stayner et al. (1993). In the extended follow-up study through 1998 (Steenland et al., 2004), the cohort averaged 26.8 years of follow-up and 16% of the cohort had died.

In the original mortality study, statistically significant trends were observed in mortality from all lymphohematopoietic cancers, non-Hodgkin lymphoma (NHL), and "lymphoid" cancers (NHL and lymphocytic leukemia) for cumulative EtO exposure using the Cox proportional hazards model, with lag periods from 5 to 10 years, driven by the excesses observed in males (Stayner et al., 2003). Positive trends were also observed in the extended follow-up, but they were slightly weaker and limited to males (Steenland et al., 2004). In the extended follow-up, the overall standard mortality ratio (SMR) for lymphohematopoietic cancer was 1.0, based on 79 cases. In categorical life-table analysis of the data, men with >13,500 ppm-days of cumulative exposure had an SMR of 1.46 (Obs = 13). For female workers, no positive exposure-response trends were seen. In internal Cox regression analyses (i.e., analyses in which the referent population is within the cohort) with exposure as a continuous variable, statistically significant trends in males for all lymphohematopoietic cancer ($p = 0.02$) and for "lymphoid" cancers (updated to include NHL, lymphocytic leukemia, and myeloma; $p = 0.02$) were observed using log cumulative exposure (ppm × days) with a 15-year lag. In internal categorical analyses, statistically significant odds ratios (ORs) were observed in the highest cumulative exposure quartile (with a 15-year lag) in males for all lymphohematopoietic cancer (OR = 3.42; 95% CI = 1.09–10.73) and "lymphoid" cancer (OR = 3.76; 95% CI = 1.03–13.64).

Although the overall SMR for female breast cancer was 0.99, based on 102 deaths, the NIOSH mortality follow-up study (Steenland et al., 2004) reported a significant excess of breast cancer mortality in the highest cumulative exposure quartile using a 20-year lag period compared to the U.S. population (SMR = 2.07; 95% CI = 1.10–3.54; Obs = 13). Internal exposure-response analyses also noted a significant positive trend for breast cancer mortality using the log of cumulative exposure and a 20-year lag time ($p = 0.01$). In internal categorical analyses, a statistically significant OR for breast cancer mortality was observed in the highest cumulative exposure quartile with a 20-year lag (OR = 3.13; 95% CI = 1.42–6.92).

The NIOSH cohort was also used for a study of breast cancer incidence and exposure to EtO (Steenland et al., 2003). The researchers identified 7,576 women from the initial cohort who had been employed in the commercial sterilization facilities for at least 1 year. Breast cancer incidence was determined from interviews (questionnaires), death certificates, and cancer registries. Interviews were obtained for 5,139 women. The main reason for non-response was inability to locate the study subject. For the full study cohort, 319 incident breast cancer cases were identified. Overall, the standard incidence ratio (SIR) was 0.87 using Surveillance, Epidemiology, and End Results (SEER) reference rates for comparison. Results with the full cohort are expected to be underestimated, however, because of case under ascertainment in the women without interviews. A significant exposure-response trend was observed for SIR across cumulative exposure quintiles, using a 15-year lag time ($p = 0.002$). In internal Cox regression analyses, with exposure as a continuous variable, a significant trend for breast cancer incidence was obtained for log cumulative exposure with a 15-year lag ($p = 0.05$), taking age, race, and year of birth into account. In the Cox regression analysis with categorical exposures and a 15-year lag, the top cumulative exposure quintile had a statistically significant OR for breast cancer incidence of 1.74 (95% CI = 1.16–2.65).

In the sub-cohort with interviews, 233 incident breast cancer cases were identified. Information on various risk factors for breast cancer was also collected in the interviews, but only parity and breast cancer in a first-degree relative turned out to be important predictors of breast cancer incidence. In internal analyses, both the cumulative exposure and log cumulative exposure models yielded significant regression coefficients with a 15-year lag ($p = 0.02$ and $p = 0.03$, respectively), taking age, race, year of birth, parity, and breast cancer in a first-degree relative into account. In the Cox regression analysis with categorical exposures and a 15-year lag, the top cumulative exposure quintile had a statistically significant OR of 1.87 (95% CI = 1.12–3.10).

Steenland et al. (2003) suggest that their findings are not conclusive of a causal association between EtO exposure and breast cancer incidence because of inconsistencies in exposure-response trends, possible biases due to non-response, and an incomplete cancer ascertainment. Although that conclusion seems appropriate, those concerns do not appear to be major limitations. As noted by the authors, it is not uncommon for positive exposure-response trends not to be strictly monotonically increasing, conceivably due to random fluctuations or imprecision in exposure estimates. Furthermore, the consistency of results between the full study cohort, which is less subject to non-response bias, and the sub-cohort with interviews, which should have full case ascertainment, alleviates some of the concerns about those potential biases.

In summary, the NIOSH investigators found significant exposure-response relationships

between exposure to EtO and lymphohematopoietic cancer mortality in males, as well as breast cancer mortality and incidence in females. These studies are the most useful of the epidemiologic studies in terms of carrying out quantitative risk assessment. They possess more attributes than the others for performing risk analysis (e.g., better estimates of individual exposure, lack of exposure to other chemicals, and a large and diverse distribution of workers).

Other epidemiologic studies provide supporting evidence of these associations; however, most of these studies have serious limitations, including small numbers of deaths (or cases), co-exposures to other chemicals, lack of individual EtO exposure estimates, and reliance on external comparisons. Other epidemiologic studies of EtO are discussed in the Carcinogenicity Assessment (U.S. EPA, 2011, Section 3.1 and Appendix A).

To summarize the epidemiological database on EtO, most of the human studies suggest an increased risk of lymphohematopoietic cancers, but the total weight of the epidemiological evidence does not provide conclusive proof of causality. Of the seven criteria of causality envisioned by Hill (1965), temporality, coherence, and biological plausibility are clearly satisfied. There is also evidence of consistency in the response, of a dose-response relationship (biological gradient), and of specificity when the loosely defined blood malignancies are combined under the rubric "cancer of the lymphohematopoietic system." On the other hand, most of the relative risk estimates are not large (strong) in magnitude.

The large NIOSH study (Steenland et al., 1991, 2004; Stayner et al., 1993) of workers at 14 chemical plants around the country provides the strongest evidence of carcinogenicity. A statistically significant positive trend was observed in the risk of lymphohematopoietic neoplasms with increasing (log) cumulative exposure to EtO, although reportedly only in males (the sex difference is not statistically significant, however, and the trend for both sexes combined is statistically significant; see U.S. EPA, 2011, Appendix D). Furthermore, for these sterilization workers, exposures to other chemicals in the workplace were believed to be minimal or nonexistent. Despite limitations in the data, most other epidemiologic studies have also found elevated risks of lymphohematopoietic cancer from exposure to EtO, although in some of these studies, confounding by other chemical exposures cannot be ruled out. The studies that suggest the absence of a significant carcinogenic effect have major limitations that make their findings inconclusive.

In addition, there is evidence of an increase in the risk of both breast cancer mortality and incidence in women who are exposed to EtO. Studies have reported increases in the risk of breast cancer in women employees of commercial sterilization plants (Steenland et al., 2003, 2004; Norman et al., 1995) as well as in Hungarian hospital workers exposed to EtO (Kardos et al., 2003). In several other studies with female employees, no elevated risks of breast cancer were reported; however, these studies had far fewer cases to analyze than the NIOSH studies, did not have individual exposure estimates, and relied on external comparisons. The Steenland et al. (2003, 2004) studies, on the other hand, used the largest cohort of women potentially exposed to EtO and clearly show significantly increased risks of breast cancer incidence and mortality based upon internal exposure-response analyses.

___II.A.3. ANIMAL CARCINOGENICITY DATA

There is strong evidence of EtO-induced cancer in laboratory animals: in both rats and

mice, in both males and females, and in multiple tissues (lung, stomach, mammary gland, uterus, lymphoid cells, brain, tunica vaginalis testis). The relevant bioassays are discussed briefly below. See the Carcinogenicity Assessment of EtO for further details (U.S. EPA, 2011, Section 3.2).

One study of oral administration in rats has been published; there are no oral studies in mice. Dunkelberg (1982) administered EtO in vegetable oil to groups of 50 Sprague-Dawley rats by gastric intubation twice weekly for 107 weeks. There were two control groups (untreated and oil gavage) and two treated groups (7.5 and 30 mg/kg/day). A dose-dependent increase in the incidence of malignant tumors in the forestomach was observed in the treated groups.

One inhalation assay was reported in mice (NTP, 1987) and two inhalation assays were reported in rats (Lynch et al., 1982, 1984, in males; Snellings et al., 1984; Garman et al., 1985, 1986, in both males and females). In the NTP mouse bioassay (NTP, 1987), groups of 50 male and 50 female $B6C3F_1$ mice were exposed to EtO via inhalation at concentrations of 0, 50, and 100 ppm for 6 hours per day, 5 days per week, for 102 weeks. A concentration-dependent increase in the incidence of tumors at several sites was induced in both sexes. Males had carcinomas and adenomas in the lung and cystadenomas in the Harderian glands. Females had carcinomas and adenomas in the lung, malignant lymphomas, adenocarcinomas in the uterus, adenocarcinomas in the mammary glands, and cystadenomas in the Harderian glands.

In the Lynch et al. (1982, 1984) bioassay in male Fischer 344 (F344) rats, groups of 80 animals were exposed to EtO via inhalation at concentrations of 0, 50, and 100 ppm for 7 hours per day, 5 days per week, for 2 years. Concentration-dependent increases in the incidence of mononuclear cell leukemia in the spleen, peritoneal mesothelioma in the testes, and glioma in the brain were observed.

In the bioassay conducted by Snellings et al. (1984), groups of 120 male and 120 female F344 rats were exposed to EtO via inhalation at concentrations of 0, 10, 33, and 100 ppm for 6 hours per day, 5 days per week, for 2 years, with scheduled kills at 6, 12, and 18 months. In males, concentration-dependent increases in the incidence of mononuclear cell leukemia in the spleen and peritoneal mesothelioma in the testes were observed, and in females an increase in mononuclear cell leukemia in the spleen was seen. In later publications describing brain tumors (Garman et al., 1985, 1986), both males and females had a concentration-dependent increased incidence of brain tumors. Note that these investigators observed the same types of tumors (splenic mononuclear cell leukemia, peritoneal mesothelioma in the testes, and brain tumors) seen by Lynch et al. (1982, 1984) in male rats.

In conclusion, EtO causes cancer in laboratory animals. After inhalation exposure to EtO, statistically significant increased incidences of cancer have been observed in both rats and mice, in both males and females, and in multiple tissues (lung, mammary gland, uterus, lymphoid cells, brain, tunica vaginalis testis). In addition, one oral study in rats has been conducted, and a significant dose-dependent increase in carcinomas of the forestomach was reported.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

EtO is a direct-acting alkylating agent that has exhibited positive genotoxic activity in a variety of biological systems, spanning the range from bacteriophage to plants to animals,

including occupationally exposed humans. The evidence of the genotoxic potential of EtO is briefly highlighted here. For more details, see the Carcinogenicity Assessment of EtO (U.S. EPA, 2011, Section 3.3.3 and Appendix C).

EtO has been shown to form a number of DNA adducts in rodents, the predominant one being N7-(2-hydroxyethyl)guanine (N7-HEG). In experiments with rats and mice exposed to EtO at concentrations in the range of those used in the cancer bioassays, Walker et al. (1992) measured increased N7-HEG adduct levels in the DNA of a variety of tissues, including targets of EtO-induced carcinogenicity. Two studies provide evidence of N7-HEG DNA adduct formation in human populations occupationally exposed to EtO, one reporting a modest increase in white blood cells (van Delft et al., 1994) and the other a four- to five-fold increase in granulocytes (Yong et al., 2007) compared to unexposed controls. However, these differences were not statistically significant due to high inter-individual variation in adduct levels. EtO has also been shown to form hemoglobin adducts in rats, mice, and humans (U.S. EPA, 2011, Section 3.3.2).

EtO has consistently yielded positive results in in vitro mutation assays from bacteriophage, bacteria, fungi, yeast, insects, plants, and mammalian cell cultures (including human cells). In prokaryotes and lower eukaryotes, EtO induces DNA damage and gene mutations in bacteria, yeast, and fungi and gene conversions in yeast. In mammalian cells, EtO-induced effects include unscheduled DNA synthesis, gene mutations, sister chromatid exchanges (SCEs), micronuclei, and chromosomal aberrations.

The results of in vivo studies on the mutagenicity of EtO have also been consistently positive following ingestion, inhalation, or injection (e.g., Tates et al., 1999). Increases in the frequency of gene mutations in T-lymphocytes (*Hprt* locus) (Walker et al., 1997) and in bone marrow and testes (*LacI* locus) (Recio et al., 2004) have been observed in transgenic mice exposed to EtO via inhalation at concentrations similar to those in carcinogenesis bioassays with this species (NTP, 1987). At somewhat higher concentrations than those used in the carcinogenesis bioassays (200 ppm, but for only 4 weeks), increases in the frequency of gene mutations have been observed in the lung of transgenic mice (*LacI* locus) (Sisk et al., 1997) and in T-lymphocytes of rats (*Hprt* locus) (Tates et al., 1999; van Sittert et al., 2000). In in vivo studies with male mice, EtO also causes heritable mutations and other effects in germ cells (Lewis et al., 1986; Generoso et al., 1990).

In a study of *p53* (tumor suppressor gene) and *Hras* (oncogene) mutations in mammary gland carcinomas of EtO-exposed and control mice, Houle et al. (2006) noted that the EtO-induced tumors exhibited a distinct shift in the mutational spectra of the *p53* and *Hras* genes and more commonly displayed concurrent mutations of the two genes. In a similar study of *Kras* (oncogene) mutations in lung, Harderian gland, and uterine tumors, substantial increases were observed in *Kras* mutation frequencies in the tumors from the EtO-exposed mice (Hong et al., 2007).

Only a few studies have investigated gene mutations in people occupationally exposed to EtO, but these studies were not conclusive due to low statistical power and other limitations.

Several inhalation studies in laboratory animals have demonstrated that EtO exposure levels in the range of those used in the rodent bioassays induce SCEs in vivo (see Table 11 of IARC, 2008); however, evidence for micronuclei and chromosomal aberrations from these same exposure levels is less consistent. In particular, studies by van Sittert et al. (2000) and Lorenti

Garcia et al. (2001) observed increases in micronuclei and chromosomal aberrations in splenic lymphocytes of rats exposed to 50, 100, or 200 ppm EtO for 6 hours/day, 5 days/week, for 4 weeks compared to levels from control rats, but the increases were not statistically significant. IARC (2008) noted, however, that "strong conclusions cannot be drawn" from these two studies because the cytogenetic analyses "were initiated 5 days after the final day of exposure, a suboptimal time, and the power of the [FISH] studies were limited by analysis of only a single chromosome and the small numbers of rats per group examined", which was 3 per exposure group in both of the studies, although numerous cells/rat were examined. Moreover, a recent study by Donner et al. (2010) showed clear, statistically significant increases in chromosomal aberrations with longer durations of exposure (≥ 12 weeks) to the concentration levels used in the rodent bioassays.

In humans, numerous studies have observed increased SCEs in occupationally exposed workers, especially for workers with the highest exposures (e.g., Sarto et al., 1987, 1991; Tates et al., 1991; Major et al., 1996). Several studies have also reported increased micronucleus formation in lymphocytes (Tates et al., 1991; Ribeiro et al., 1994), in nasal mucosal cells (Sarto et al., 1990), and in bone marrow cells (Hogstedt et al., 1983), although this endpoint seems to be less sensitive than SCEs. An association between increased micronucleus frequency and cancer risk has been reported in at least one large prospective general population study (Bonassi et al., 2007). In addition, chromosomal aberrations have been reported in multiple studies of workers occupationally exposed to EtO (Sarto et al., 1987; Tates et al., 1991; Ribeiro et al., 1994). Chromosomal aberrations have been linked to an increased risk of cancer in several large prospective general population studies (e.g., Hagmar et al., 2004; Rossner et al., 2005; Boffetta et al., 2007).

The available data from in vitro studies, experimental animal studies, and human studies establish that EtO is both a mutagen and a genotoxicant. Furthermore, the weight of evidence is sufficient to support a mutagenic mode of action for EtO carcinogenicity (U.S. EPA, 2011, Section 3.4). The key events in the mutagenic mode of action are DNA adduct formation by EtO, which is a direct-acting alkylating agent, and the resulting genetic damage, including the formation of point mutations as well as chromosomal alterations. Mutagenicity is a well established cause of carcinogenicity.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

NOT AVAILABLE. The carcinogenic effects of oral exposure to EtO have not been evaluated (U.S. EPA, 2011).

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

____II.C.1.1. Inhalation Unit Risk – EPA has concluded, by a weight-of-evidence evaluation, that EtO is carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (*Supplemental Guidance*) (U.S. EPA, 2005b), those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for EtO are not sufficient to develop separate risk estimates for childhood exposure. The inhalation unit risk of 1.1×10^{-3} per $\mu g/m^3$, calculated from data from adult exposure, does not reflect presumed increased early-life susceptibility for this chemical and age-dependent adjustment factors (ADAFs) should be applied to this unit risk when assessing cancer risks. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance*. For *full lifetime* exposure to a constant exposure level, the ADAF-adjusted unit risk estimate for EtO is 1.8×10^{-3} per $\mu g/m^3$ (U.S. EPA, 2011, Section 4.4).

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). The 10-fold and 3-fold adjustments in unit risk are to be combined with age-specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to EtO. These ADAFs and their age groups were derived from the *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for EtO, age-specific values for cancer potency are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance*).

The inhalation unit risk for EtO, calculated from adult exposure, is equivalent to the risk (as a fraction, i.e., 0.01 here) divided by the LEC_{01}, the 95% lower bound on the exposure associated with a 1% extra cancer risk, and represents an upper bound risk estimate for lifetime risk from continuous adulthood exposure without consideration of early-life exposures and increased early-life susceptibility due to EtO's mutagenic mode of action. A 1% extra risk level is used for the determination of the point of departure (POD) for low-exposure extrapolation because the exposure-response analysis is based on epidemiological data, which normally demonstrate lower cancer response rates than rodent bioassays; an LEC_{10} is not calculated because it would involve an upward extrapolation for these data.

Adult-based inhalation unit risk estimate - 1.1×10^{-3} per $\mu g/m^3$
Full lifetime unit risk estimate - 1.8×10^{-3} per $\mu g/m^3$

Adult-based LEC_{01}, lower 95% bound on exposure at 1% extra risk - 9.2 $\mu g/m^3$
Adult-based EC_{01}, central estimate of exposure at 1% extra risk – 16 $\mu g/m^3$

The slope of the linear extrapolation from the adult-based central estimate EC_{01} is

$0.01/(16\ \mu g/m^3) = 6.3 \times 10^{-4}$ per $\mu g/m^3$.

The unit risk for EtO should not be used with exposures exceeding 100 $\mu g/m^3$, because above this level the linear exposure-response model no longer provides a good representation of the exposure-response data for EtO (U.S. EPA, 2011, Section 4.5). Additionally, ADAFs should be applied to this unit risk when assessing cancer risks to individuals exposed in early life (i.e., <16 years old), as discussed above (U.S. EPA, 2005).

Air Concentrations at Specified Risk Levels

Air concentrations at specified risk levels for EtO are calculated from the full lifetime ADAF-adjusted unit risk estimate, assuming ppm equivalence across age groups (i.e., risk is proportional to air concentration, independent of size, or age), as is commonly assumed for air toxicants that act systemically.

Air Concentrations at Specified Risk Levels:

Risk Level	Lower Bound on Concentration Estimate
E-4 (1 in 10,000)	0.06 $\mu g/m^3$
E-5 (1 in 100,000)	0.006 $\mu g/m^3$
E-6 (1 in 1,000,000)	0.0006 $\mu g/m^3$

____II.C.1.2. Exposure-Response Model and Extrapolation Method

Linear regression of categorical results (excluding the highest exposure group) for lymphoid cancers and 2-piece linear spline model for breast cancers, with linear extrapolation from the PODs (LEC_{01}s). The unit risk estimates for the 2 tumor types were then combined assuming that the tumor types are independent and that the risk estimates are approximately normally distributed.

___II.C.2. DOSE-RESPONSE DATA

For lymphoid cancer: Cox regression results for lymphoid cancer mortality in both sexes for cumulative exposure, 15-year lag; data from the NIOSH occupational epidemiology study (Steenland et al., 2004), with additional analyses by Dr. Steenland (U.S. EPA, 2011, Appendix D)*:

Mean Exposure (ppm × days)	Odds Ratio (95% CI)
0	1.00
446	1.75 (0.59–5.25)
2143	3.15 (1.04–9.49)
7335	2.44 (0.80–7.50)

39927	3.00 (1.02–8.45)

* cases and controls matched on sex, race, year of birth; 53 cases

The highest exposure quartile (13 cases) was excluded from the linear regression model because of the supralinearity of the data. Incidence risk estimates (LEC_{01} and EC_{01}) were obtained from the mortality data using a lifetable analysis. See the Carcinogenicity Assessment for EtO (U.S. EPA, 2011, Section 4.1.1) for more details on the derivation of unit risk estimates from the lymphoid cancer data.

For (female) breast cancer: A 2-piece linear spline model was used for exposure-response modeling of the individual data from the sub-cohort with interviews from the Steenland et al. (2004) breast cancer incidence study with exposure as a continuous variable (U.S. EPA, 2011, Section 4.1.2 and Appendix D). A regression coefficient of 0.000119 per ppm × day (SE = 0.0000677 per ppm × day) was obtained for the low-exposure spline segment. A lifetable analysis was conducted to estimate the LEC_{01} and EC_{01} from the exposure-response model.

___II.C.3. ADDITIONAL COMMENTS

As discussed above, because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and in the absence of chemical-specific data to evaluate differences in susceptibility, early-life susceptibility is assumed and the ADAFs should be applied to the adult-based unit risk estimate, in accordance with the *Supplemental Guidance* (U.S. EPA, 2005b).

The adult-based unit risk estimate presented above (1.1×10^{-3} per $\mu g/m^3$) is for total cancer incidence, reflecting the incidence risks for both lymphoid cancers and breast cancer. The adult-based unit risk estimates for the separate cancer types were 4.3×10^{-4} per $\mu g/m^3$ for lymphoid cancer incidence and 8.2×10^{-4} per $\mu g/m^3$ for breast cancer incidence.

Extra risk estimates for some occupational exposure scenarios were also computed based on the NIOSH occupational epidemiology data and are presented in Section 4.7 of the Carcinogenicity Assessment for EtO (U.S. EPA, 2011).

An alternative dose-squared model presented by the Ethylene Oxide Industry Council (EOIC, 2001; Kirman et al., 2004) was considered but judged to be not appropriate for this assessment (U.S. EPA, 2011, Sections 3.4 and 4.6.1).

Finally, unit risk estimates were calculated from the three rodent bioassays for comparison; these ranged from 2.2×10^{-5} to 4.6×10^{-5} per $\mu g/m^3$ (U.S. EPA, 2011, Section 4.2).

___II.C.4. DISCUSSION OF CONFIDENCE

Some primary sources of uncertainty in the unit risk estimates are discussed briefly below. See the Carcinogenicity Assessment for EtO (U.S. EPA, 2011, Section 4.1.4) for a more comprehensive discussion of sources of uncertainty.

The two major sources of uncertainty in quantitative cancer risk estimates are generally interspecies extrapolation and high-dose to low-dose extrapolation. The risk estimates presented here are not subject to interspecies uncertainty because they are based on human data.

Uncertainty remains in the extrapolation from occupational exposures to lower environmental exposures. Although the actual exposure-response relationship at low exposure levels is unknown, the unequivocal evidence of EtO mutagenicity supports the linear low-exposure extrapolation that was used (U.S. EPA, 2005a).

Other sources of uncertainty emanate from the epidemiologic studies and their analyses (Steenland et al., 2003, 2004; Steenland analyses in Appendix D), including the retrospective estimation of EtO exposures in the cohort, the modeling of the epidemiologic exposure-response data, the proper dose metric for exposure-response analysis, and potential confounding or modifying factors. Although these are common areas of uncertainty in epidemiologic studies, they were generally well addressed in the NIOSH studies.

Regarding exposure estimation, the NIOSH investigators conducted a detailed retrospective exposure assessment to estimate the individual worker exposures. They used extensive data from 18 facilities, spanning a number of years, to develop a regression model (Greife et al., 1988; Hornung et al., 1994). The model accounted for 85% of the variation in average EtO exposure levels. While the NIOSH regression model performed well in estimating exposures in validation tests (Hornung et al., 1994), there is uncertainty associated with any retrospective exposure assessment, and this could affect the ability to discriminate among exposure-response models.

With respect to the lymphohematopoietic cancer response, analyses were done for both lymphoid cancers and all lymphohematopoietic cancers (Steenland et al., 2004). The associations observed for all lymphohematopoietic cancers was largely driven by the lymphoid cancer responses, and, biologically, there is stronger support for an etiologic role for EtO in the development of the more closely related lymphoid cancers than in the development of the more diverse cancers in the aggregate all lymphohematopoietic cancer grouping; thus, the lymphoid cancer analysis is the preferred analysis for the lymphohematopoietic cancers. Nonetheless, the unit risk estimate for all lymphohematopoietic cancers was similar (about 50% greater) to that for the lymphoid cancers.

For the lymphoid cancer response (Steenland et al., 2004), modeling of the exposure-response is limited by the number of cases (n = 53). The Cox proportional hazards model used by Steenland et al. is commonly used for this type of analysis because exposure can be modeled as a continuous variable, competing causes of mortality can be taken into account, and potential confounding factors can be controlled for in the regression. However, the log cumulative exposure Cox regression model with 15-year lag, which provides the best fit (in terms of lowest p-value; see U.S. EPA [2011], Appendix D, for additional results based on both sexes) to the overall data, is very steep in the low-exposure region and then plateaus rapidly at higher exposures, making it difficult to derive stable unit risk estimates (i.e., estimates that are not highly dependent on the POD) for environmental exposures. The alternative cumulative exposure model, though typically used for epidemiologic data, is too sub-linear in the low-exposure region for these data, which exhibit supralinearity (i.e., a concave-down response pattern). Two-piece log-linear and linear spline models were fit to the individual continuous data to address the supralinearity of the data while avoiding the extreme low-exposure curvature of the log cumulative exposure model; however, these models also resulted in low-exposure slopes that appeared to be implausibly steep. Due to small numbers of cancer cases in the low exposure range there is little confidence in the resulting steep low-exposure slopes. Therefore, a weighted

linear regression model based on the Cox regression categorical results, using the first three quartiles of the categorized data, was used to model the exposure-response relationship in the exposure region below the point where the relationship "plateaus". The linear model is a parsimonious choice which assumes neither a sublinear nor a supralinear exposure-response relationship and is suitable to represent these data. The highest categorical exposure group was not included in the estimation because its inclusion would have resulted in a slope that would have underestimated the apparent low-exposure risks.

Although EPA believes the linear regression model is a reasonable and sound approach for modeling the exposure-response results at the lower end of the exposure range, there is uncertainty regarding the exposure-response model. The log cumulative exposure Cox regression model, which was the best-fitting model overall, yields much lower EC_{01} and LEC_{01} estimates, but the estimates based on the linear regression model are preferred because the linear regression model is substantially more stable.

Several dose metrics (cumulative exposure, duration of exposure, maximum [8-hour TWA] exposure, and average exposure) were analyzed by the Steenland et al. (2004), and cumulative exposure was the best predictor of mortality from lymphoid cancers. Cumulative exposure is considered a good measure of total exposure because it integrates exposure (levels) over time.

Also, the important potential modifying/confounding factors of age, sex, race, and calendar time were taken into account in the analysis, and the plants included in this cohort were specifically selected for the absence of any known confounding exposures (Stayner et al., 1993).

With respect to the breast cancer response, Steenland et al. (2003) conducted an incidence study for breast cancer; therefore, it was not necessary to calculate unit risk estimates for breast cancer incidence indirectly from the mortality data as was done for lymphoid cancers. From the incidence study, the subcohort with interviews was preferred for deriving risk estimates because the full cohort had incomplete case ascertainment, the subcohort retained a substantial number of cases (233), and the subcohort had additional information on personal breast cancer risk factors. For the subcohort, the cumulative exposure and log cumulative exposure Cox regression models fit nearly equally well. For both groups, the categorical Cox regression results suggest that a linear model lying between the supralinear log cumulative exposure model and the sublinear cumulative exposure model would better represent the low-exposure data than either of the two presented continuous-variable models. In subsequent analyses by Dr. Steenland (U.S. EPA, 2011, Appendix D) of the full set of individual data using exposure as a continuous variable, two-piece log-linear and two-piece linear spline models were used to model the subcohort data; the two-piece linear spline model was the best-fitting of these models and provided the preferred breast cancer incidence risk estimates. There was, however, substantial variation in the EC_{01} estimates obtained from the different models (log cumulative, cumulative, and two-piece linear spline), reflecting exposure-response model uncertainty.

With respect to the two-piece spline models, the use of this model form is not intended to imply that an abrupt change in biological response occurs at the knot (or inflection point), but, rather, to allow description of an exposure-response relationship in which the slope of the relationship differs markedly in the low-exposure versus high-exposure regions. The two-piece model is used here primarily for its representation of the low-exposure data. The main uncertainty in the two-piece spline models is in the selection of the knot, and the location of the

knot is critical in defining the low-exposure slope. The model likelihood was used to provide a statistical basis for knot selection; although, as shown in Appendix D, the likelihood did not generally change appreciably over a range of possible knots. Thus, because of the importance of knot selection, a sensitivity analysis was done to examine the impacts of selecting different knots (Section 6 of Appendix D). For the sensitivity analysis, the two-piece log-linear model was run with knots roughly one increment (1000 ppm × days) below and one increment above the selected knot. For breast cancer incidence, this sensitivity analysis yielded EC_{01} estimates about 14% lower and 14% higher, respectively, than the EC_{01} estimate obtained with the originally selected knot of 6000 ppm × days.

With respect to dose metrics for breast cancer incidence, models using duration provided model fits with lower p-values than those using cumulative exposure (Steenland et al., 2003); however, duration is less useful for estimating unit risks and the cumulative exposure models also provided statistically significant fits to the data, thus the cumulative exposure metric was used for the quantitative risk estimates. Models using peak or average exposure did not fit as well.

Regarding potential confounders/modifying factors, a number of specific breast cancer risk factors were investigated for the subcohort with interviews, including body mass index, breast cancer in a first-degree relative, parity, age at menopause, age at menarche, socioeconomic status, and diet; however, only parity and breast cancer in a first-degree relative were determined to be important predictors of breast cancer and were included in the final models. Thus, analyses for the subcohort were adjusted for age, race, calendar time, breast cancer in a first-degree relative, and parity. Furthermore, exposures to other chemicals in these plants were reportedly minimal, so confounding from other workplace exposures is unlikely.

Some additional sources of uncertainty are not so much inherent in the exposure-response modeling or in the epidemiologic data themselves but, rather, arise in the process of obtaining more general Agency risk estimates from the epidemiologic results. EPA cancer risk estimates are typically derived to represent an upper bound on increased risk of cancer incidence for all sites affected by an agent for the general population. In deriving such risk estimates from the NIOSH epidemiologic data, certain limitations are encountered. First, the study reported by Steenland et al. (2004) is a retrospective mortality study, and cancer incidence data are not available for the lymphohematopoietic cancers (for breast cancer, a separate incidence study [Steenland et al., 2003] was available). Second, these occupational epidemiology data represent a healthy-worker cohort. Third, the epidemiologic study may not have sufficient statistical power and follow-up time to observe associations for all the tumor sites that may be affected by EtO.

The first limitation was addressed quantitatively in the life-table analysis for the lymphoid cancer risk estimates. Although assumptions are made in using incidence rates for the cause-specific background rates (U.S. EPA, 2011, Section 4.1.1.3), the resulting incidence-based estimates are believed to be better estimates of cancer incidence risk than are the mortality-based estimates. Because of the relatively high survival rates for lymphoid cancers, the incidence unit risk estimate is about 120% higher than (i.e., 2.2 times) the mortality-based estimate.

The healthy-worker effect is often an issue in occupational epidemiology studies, but the internal exposure-response analyses conducted by these investigators help address this concern, at least partially. In terms of representing the general population, the NIOSH study cohort was

relatively diverse. It contained both female (55%) and male workers, and the workers were 79% white, 16% black, and 5% "other." Furthermore, because of EtO's mutagenic mode of action, increased early-life susceptibility is assumed and ADAFs are applied for exposure scenarios involving early life.

With respect to other possible tumor sites of concern, the rodent data suggest that lymphohematopoietic cancers are a major tumor type associated with EtO exposure in female mice and in male and female rats. Thus, it is reasonable that this might be a tumor type of concern in humans, too. Likewise, the mouse data suggest an increased risk of mammary gland tumors from EtO exposure, and evidence of that can be seen in the Steenland et al. (2003, 2004) study. However, the rodent data suggest associations between EtO exposure and other tumor types as well, and, although site concordance across species is not generally assumed, it is possible that the NIOSH study, despite its relatively large size and long follow-up (mean length of follow-up was 26.8 years), had insufficient power to observe small increases in risk in certain other sites. For example, the tumor site with the highest potency estimate in both male and female mice was the lung. In the NIOSH study, one cannot rule out a small increase in the risk of lung cancer, which has a high background rate.

To obtain the risk estimate for total cancer risk, the estimates for lymphoid cancer incidence and breast cancer incidence were combined. The approach used to combine estimates for different sites assumes a normal distribution of risk estimates. While there are uncertainties in this approach, the resulting unit risk estimate is appropriately bounded in the roughly 2-fold range between estimates based on the sum of the individual MLEs of risk and the sum of the individual 95% UCLs, and, thus, any inaccuracy in the total cancer unit risk estimate resulting from the approach used is relatively minor. Because the breast cancer component of the total cancer risk estimate applies only to females, the total cancer risk estimate is expected to overestimate the cancer risk to males somewhat (the preferred unit risk estimate for lymphoid cancer alone was about 40% of the total cancer risk estimate).

Despite these uncertainties, the inhalation cancer unit risk estimate has the advantages of being based on human data from a high-quality epidemiologic study with individual exposure estimates for each worker. Furthermore, the breast cancer component of the risk estimate, which contributes approximately 60% of the total cancer risk, is based on a substantial number of incident cases [233 total, the vast majority of which were in the exposure range below the knot in the 2-piece linear spline model].

In addition to the uncertainties discussed above for the inhalation unit risk estimate, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The ADAFs reflect an expectation of increased risk from early-life exposure to carcinogens with a mutagenic mode of action (U.S. EPA, 2005b), but they are general adjustment factors and are not specific to EtO.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- _____

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix H of the *Evaluation of the Carcinogenicity of Ethylene Oxide* (U.S. EPA, 2011).

___II.D.2. EPA REVIEW

Agency Completion Date -- __/__/__

___II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name – Ethylene Oxide
CASRN -- 75-21-8
Section VI. Last Revised -- 00/00/0000

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_VII. REVISION HISTORY

Substance Name – Ethylene Oxide
CASRN -- 75-21-8
File First On-Line __/__/__

Date	Section	Description
00/00/0000		

_VIII. SYNONYMS

Substance Name – Ethylene Oxide
CASRN -- 75-21-8
Section VIII. Last Revised -- 00/00/0000

E O
AETHYLENOXID (GERMAN)
AI3-26263
Amprolene
ANPROLENE
Anproline
Caswell no 443
DIHYDROOXIRENE
DIMETHYLENE OXIDE
ENT-26263
USEPA/OPP Pesticide Code: 042301
EPA pesticide chemical code 042301
Epoxyethane
1,2-EPOXYETHANE
Ethene oxide
Ethox
ETO
ETYLENU TLENEK (POLISH)
Fema no 2433
T-GAS
NCI-C50088
OXACYCLOPROPANE
OXANE
OXIDOETHANE
ALPHA,BETA-OXIDOETHANE
OXIRAAN (DUTCH)
OXIRAN
OXIRANE

OXIRENE, DIHYDRO-
OXYFUME
OXYFUME 12