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External Review Draft

Evaluation of the Carcinogenicity of Ethylene Oxide

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PREFACE

This document is the U.S. Environmental Protection Agency's (EPA's) external review draft of the evaluation of the carcinogenicity of ethylene oxide (EtO). The assessment was prepared by the National Center for Environmental Assessment, which is the health risk assessment program in the Office of Research and Development. The assessment broadly supports activities authorized in the 1990 Clean Air Act and is of particular interest to EPA's Office of Air and Radiation. However, this review also should be applicable to the needs of all program Offices and Regions in evaluating the carcinogenicity of EtO.

EPA last published a health assessment of the potential carcinogenicity of EtO in 1985 (U.S. EPA, 1985). The current assessment reviews the more recent database on the carcinogenicity of EtO, pertinent data from the 1985 assessment, and several reviews and assessments issued by other organizations (IARC, 1994; Health Canada, 2001; CalEPA, 1999; EOIC, 2001). This document was preceded by an internal review draft (NCEA-W-1341). The scientific literature search for this assessment is generally current through June 2004, although a few later publications are included. This assessment focuses on lifetime cancer risk from inhalation exposure.

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1. EXECUTIVE SUMMARY

Ethylene oxide (EtO) is a gas at room temperature. It is manufactured from ethylene and used primarily as a chemical intermediate in the manufacture of ethylene glycol. It is also used as a sterilizing agent for medical equipment and as a fumigating agent for spices. The largest sources of human exposure are in occupations involving contact with the gas in plants (facilities) and in hospitals that sterilize medical equipment. EtO can also be inhaled by residents living near production or sterilizing/fumigating facilities.

This review should be applicable to the needs of all program Offices and Regions in evaluating the carcinogenicity of EtO. EPA last published a health assessment of the potential carcinogenicity of EtO in 1985 (U.S. EPA, 1985). The current assessment reviews the more recent database that has developed on the carcinogenicity of EtO, pertinent data from the 1985 assessment, and several reviews and assessments issued by other organizations (IARC, 1994; Health Canada, 2001; CalEPA, 1999; EOIC, 2001; NTP, 2000). This assessment focuses on lifetime cancer risk from inhalation exposure.

The DNA-damaging properties of EtO have been studied since the 1940s. EtO is known to be mutagenic in a large number of living organisms, ranging from bacteriophage to mammals, and it also induces chromosome damage. It is carcinogenic in mice and rats, inducing tumors of the lymphohematopoietic system, brain, lung, connective tissue, uterus, and mammary gland. In humans employed in EtO-manufacturing facilities and in sterilizing facilities, the greatest evidence of a cancer risk from exposure is for cancer of the lymphohematopoietic system. Increases in the risk of lymphohematopoietic cancer have been seen in several studies, manifested as an increase either in leukemia or in cancer of the lymphoid tissue. In one large epidemiologic study of sterilizer workers that had a well-defined exposure assessment for individuals, positive exposure-response trends for lymphohematopoietic cancer mortality in males and for breast cancer mortality in females were reported (Steenland et al., 2004). The positive exposure-response trend for female breast cancer was confirmed in an incidence study based on the same worker cohort (Steenland et al., 2003).

Although the evidence of carcinogenicity from human studies was short of conclusive, EtO was characterized as carcinogenic to humans based on the total weight of evidence, in accordance with EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). Supporting information includes sufficient evidence of carcinogenicity in laboratory animals, clear evidence that EtO is genotoxic, and evidence of chromosome damage in humans exposed to EtO.

This document derives inhalation unit risk estimates for cancer mortality and incidence based on the human data. An EC_{01} of 44 $\mu g/m^3$ (0.024 ppm) was calculated using a life-table

analysis and linear modeling of the categorical Cox regression analysis results for excess lymphohematopoietic cancer mortality in males reported in a high-quality occupational epidemiologic study (Steenland et al., 2004). Linear low-dose extrapolation from the LEC_{01} yielded a lifetime extra cancer mortality unit risk estimate of 5.0×10^{-4} per $\mu g/m^3$ (0.92 per ppm) of continuous EtO exposure. Applying the same linear regression coefficient and life-table analysis to background male lymphohematopoietic cancer *incidence* rates yielded an EC_{01} of 24 $\mu g/m^3$ (0.013 ppm) and a preferred lifetime extra cancer unit risk estimate of 9.0×10^{-4} per $\mu g/m^3$ (1.6 per ppm). The preferred estimate is greater than the estimate of 5.0×10^{-4} per $\mu g/m^3$ (0.91 per ppm; EC_{01} = 44 $\mu g/m^3$) calculated, using the same approach, from the results of a breast cancer incidence study of the same worker cohort (Steenland et al., 2003), and is recommended as the potency estimate for Agency use. Although there was no clear exposure-response relationship for lymphohematopoietic cancer in females in the Steenland et al. (2004) study, an increased risk to females cannot be ruled out. Nonetheless, the Steenland et al. results suggest that if such a risk exists for females, it is likely to be lower than the risk estimated for males; thus, it is expected that the risk estimate based on lymphohematopoietic cancer in males would be protective of females, even if they have an increased risk for both breast cancer and lymphohematopoietic cancer.

Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and in the absence of chemical-specific data on early-life susceptibility, increased early-life susceptibility should be assumed and, if there is early-life exposure, the age-dependent adjustment factors (ADAFs) should be applied, as appropriate, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility From Early-Life Exposure to Carcinogens,* hereinafter referred to as "EPA's Supplemental Guidance" (U.S. EPA, 2005b). Applying the ADAFs to the unit risk estimate of 9.0×10^{-4} per $\mu g/m^3$ yields a full lifetime unit risk estimate of 1.5×10^{-3} per $\mu g/m^3$, and the commensurate lifetime chronic exposure level of EtO corresponding to an increased cancer risk of 10^{-6} is 0.0007 $\mu g/m^3$. [Note that for less-than-lifetime exposure scenarios (or for exposures that vary with age), the adult-based potency estimate of 9.0×10^{-4} per $\mu g/m^3$ should be used, in conjunction with the ADAFs as appropriate, in accordance with EPA's Supplemental Guidance.]

Unit risk estimates were also derived from the three chronic rodent bioassays for EtO reported in the literature, without considering early-life susceptibility. These estimates, ranging from 2.2×10^{-5} per $\mu g/m^3$ to 4.6×10^{-5} per $\mu g/m^3$, are about an order of magnitude lower than the estimates based on human data. The Agency takes the position that human data, if adequate data are available, provide a more appropriate basis than rodent data for estimating population risks (U.S. EPA, 2005a), primarily because uncertainties in extrapolating quantitative risks from rodents to humans are avoided. Although there is a fairly sizable difference between the rodent-

and human-based estimates, the similarity between the unit risk estimates based on the male lymphohematopoietic cancer and the female breast cancer results increases confidence in the use of the unit risk estimate based on the male lymphohematopoietic cancer results.

The unit risk estimates were developed for environmental exposure levels and are not necessarily applicable to higher-level occupational exposures, which appear to be subject to a different exposure-response relationship. However, occupational exposure levels are of concern to EPA when EtO is used as a pesticide (e.g., fumigant for spices). Therefore, this document also presents extra risk estimates for cancer for a number of occupational exposure scenarios.

2. INTRODUCTION

Ethylene oxide (EtO) is a gas at room temperature. It is manufactured from ethylene and used primarily as a chemical intermediate in the manufacture of ethylene glycol (NTP, 2000). It is also used as a sterilizing agent for medical equipment and as a fumigating agent for spices. The largest sources of human exposure are in occupations involving contact with the gas in plants (facilities) and in hospitals that sterilize medical equipment. EtO can also be inhaled by residents living near production or sterilizing/fumigating facilities.

The purpose of this document is to derive the cancer inhalation unit risk estimate for ethylene oxide (EtO). The document was prepared by the National Center for Environmental Assessment (NCEA), Office of Research and Development, for use by EPA's Office of Air Quality Planning and Standards (OAQPS), Office of Air and Radiation. EPA last published a health assessment of the potential carcinogenicity of EtO in 1985 (U.S. EPA, 1985). Under Section 112 of the 1990 Clean Air Act Amendments, the Agency is required to promulgate national standards for source categories emitting any of the 188 currently listed hazardous air pollutants (HAPs) in amounts exceeding specific emission thresholds. The initial standards were technology-based emission standards, with further requirements in Section 112(f) for EPA to consider the need for additional "residual risk" standards that would, if required, "provide an ample margin of safety to protect public health". Ethylene Oxide is one of the 188 HAPs for which the Agency is considering residual risk standards. Understanding the time frame for this risk-based regulatory decision and the evidence of EtO carcinogenicity, OAQPS and NCEA chose to put initial emphasis on the assessment of cancer hazard and dose-response.

Although OAQPS was the requesting office, this review should be applicable to the needs of other program offices and regions in evaluating the carcinogenicity of EtO. The current assessment reviews the more recent database that has developed on the carcinogenicity of EtO, pertinent data from the 1985 assessment, and several reviews and assessments issued by other

organizations (IARC, 1994; Health Canada, 2001; CalEPA, 1999; EOIC, 2001). This assessment focuses on lifetime cancer risk from inhalation exposure.

3. HAZARD IDENTIFICATION

3.1. EVIDENCE OF CANCER IN HUMANS

The literature from 1988 to present contains numerous studies of the carcinogenic effects of EtO in occupational cohorts; some of these cohorts were the subject of multiple reports. The conclusions about the human evidence of carcinogenicity in this assessment are based on the following summary of those studies, which are critically reviewed in Appendix A.

Two primary sources of exposures to EtO are production facilities and sterilization operations. There are two types of production facilities (IARC, 1994):

1. those using the older chlorohydrin process, where ethylene is reacted with hypochlorous acid and then with calcium oxide to make EtO (this method produces unwanted byproducts, the most toxic of which is ethylene dichloride), and

2. those producing EtO via direct oxidation of ethylene in a pressurized vessel, which involves less EtO exposure and eliminates the chemical byproducts of the chlorohydrin process.

Exposure in the sterilization of medical equipment and in the direct oxidation process is predominantly to EtO, whereas exposure in the chlorohydrin process is to EtO mixed with other chemicals.

Hogstedt et al. (1986) and Hogstedt (1988) summarized findings of three Swedish occupational cohorts (539 men and 170 women) exposed in a plant where hospital equipment is sterilized, in a chlorohydrin production facility, and in a direct oxidation production facility. The incidence of leukemia was elevated in all cohorts, although the risk was not statistically significant in the cohort from the direct oxidation facility. For the three cohorts combined there were statistically significantly elevated standard mortality ratios (SMRs) for leukemia (SMR = 9.2; 95% confidence interval ([CI] = 3.7–19), based on 7 deaths, and for stomach cancer (SMR = 5.5; 95% CI = 2.6–10), based on 10 deaths. Although this study produced high SMRs for leukemia, stomach cancer, and total cancer, it suffers from some limitations, such as multiple exposures to numerous other chemicals, lack of personal exposure information, and lack of latency analysis. No gender differences were separately analyzed. No dose-response calculations were possible. This study provides suggestive evidence of the carcinogenicity of EtO.

Coggon et al. (2004) reported the results of a followup study of a cohort originally studied by Gardner et al. (1989). The cohort included workers in three EtO production facilities (two using both chlorohydrin and direct oxidation processes and the third using direct oxidation only); in a fourth facility that used EtO in the manufacture of other chemicals; and in eight hospitals that used EtO in sterilizing units. The total cohort comprised 1,864 men and 1,012 women. No statistically significant excesses were observed for any cancer site. Slight increases, based on small numbers, were observed for the various lymphohematopoietic cancers: Hodgkin's disease (2 vs. 1 expected), non-Hodgkin's lymphoma (NHL) (7 vs. 4.8), multiple myeloma (3 vs. 2.5), and leukemia (5 vs. 4.6). The increases were concentrated in the 1,471 chemical-manufacturing workers, of whom all but 1 were male. In the chemical-manufacturing workers with "definite" exposure, 4 leukemias were observed (1.7 expected) and 9 lymphohematopoietic cancers were observed (4.9 expected). A slight deficit in the risk of breast cancer deaths (11 vs. 13.2) was observed in the cohort. No individual exposure measurements were obtained from cohort members, and no exposure measurements were available before 1977. Multiple exposures to other chemicals, small numbers of deaths, and lack of individual EtO measurements make this study only suggestive of a higher risk of leukemia from exposure to EtO.

A series of retrospective mortality studies of 2,174 male workers in a Union Carbide Corporation (UCC) EtO production facility in West Virginia (Greenberg et al., 1990; Teta et al., 1993, 1999; Benson and Teta, 1993) has been published. The chlorohydrin process was used from 1925 to 1957, and the direct oxidation process was used from 1937 to 1971. The cohort was observed from 1940 through 1978 in the original study (Greenberg et al., 1990) and through 1988 in the latter three studies. A large-scale industrial hygiene survey and monitoring of EtO concentrations was carried out in 1976.

Greenberg et al. (1990) found elevated but not statistically significant risks of pancreatic cancer (SMR = 1.7) and leukemia (SMR = 2.3) (each based on seven cases) in the entire cohort; most of the cases occurred in the chlorohydrin production unit. Limitations to this study included multiple exposures to many different chemicals in the facility through the years and lack of exposure measurements to EtO prior to 1976. Exposure levels prior to 1976 were assumed to be similar to those found in 1976. Three categories of exposure were established for analysis—low, intermediate, and high—based on the likelihood of the occurrence of dermatologic or other medical problems and the results of the 1976 survey. No significant findings of a dose-response relationship were discernable. No quantitative estimates of individual exposure were made in this study. With no latency analysis, there exists only the suggestion of an increased risk of cancer in this study. Furthermore, EtO is not the only chemical to which this excess mortality could be attributed.

A followup study (Teta et al., 1993) that extended the observation of direct oxidation workers only (eliminating the 278 chlorohydrin workers) for an additional 10 years to 1988, found no significant risk of total cancer; there was a slight trend in the risk of leukemia with increasing duration of assignment to departments using or processing EtO, but it was not significant and was based on five cases (see Table A-2). The same problems of exposure ascertainment exist for this study as for that of Greenberg et al. (1990). For estimates of exposure prior to 1976, levels were assumed to be the same as those at other "similar" plants. As with Greenberg et al. (1990), no latency analysis was conducted in this study, although the average followup was reported to be 27 years. Essentially, the study did not support the earlier studies of cancer in EtO workers; however, it was limited by most of the same problems as the larger Greenberg et al. study and thus could not assist in determining whether exposure to EtO was causally related to cancer.

In a parallel followup study through 1988 of only the chlorohydrin employees, Benson and Teta (1993) found that pancreatic cancer and hematopoietic cancer cases continued to accumulate and that the SMRs were statistically significant for pancreatic cancer (SMR = 5; Obs = 8, $p<0.05$) and for hematopoietic cancer (SMR = 3; Obs = 8, $p<0.05$). They interpreted these excesses as possibly due to ethylene dichloride, a byproduct in the chlorohydrin process. Again, this small study of only 278 workers was limited by the same problems as the Greenberg et al. (1990) study and the Teta et al. (1993) study. No individual estimates of exposure are available and the workers were potentially exposed to many different chemicals (Table A-3). Hence this study is marginal in determining the carcinogenicity of EtO.

In a later analysis, Teta et al. (1999) included an update of their earlier study of UCC workers (Teta et al., 1993), and they fitted dose-response models to the updated UCC data and to data from a study by the National Institute for Occupational Safety and Health (NIOSH) (described below). They reported that latency and lagging of exposure did not appreciably affect the fitted Poisson regression models to these data, which the authors assumed to be the best models for evaluating dose-response relationships. Because Teta et al. (1999) did not present aggregate risk ratios in the categories used to model dose-response relationships, the only comparison that can be made between the UCC and NIOSH data is based on the fitted models. These models are almost identical for leukemia, but for the lymphoid category, the risk—according to the fitted model for the UCC data—decreased as a function of exposure, whereas the risk for the modeled NIOSH data increased as a function of exposure. It is possible that the difference is due to geographic differences in the coding of death certificates for specific types of leukemia. The UCC workers were in West Virginia only, whereas workers in the NIOSH study were from multiple states.

In a study of 2,658 male workers at eight chemical plants where EtO is produced (manufacturing process not stated), Kiesselbach et al. (1990) found slightly increased SMRs for cancers of the stomach, esophagus, and lung. A latency analysis was done only for stomach cancer and total mortality. The investigators considered 71.6% of the cohort to be "weakly" exposed; only 2.6% were "strongly exposed." No data were provided to explain how these exposure categories were derived. The workers were followed for a median 15.5 years. Without additional information on exposure to EtO, this study is of little help at this time in determining the carcinogenicity of EtO.

NIOSH conducted an industrywide study of 18,254 workers (45% male and 55% female) in 14 plants where EtO was used (Steenland et al., 1991; Stayner et al., 1993; Steenland et al., 2004). Most of the workers were exposed while sterilizing medical supplies and treating spices and in the manufacture and testing of medical sterilizers. 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 followup study are presented in Steenland et al. (1991) and Stayner et al. (1993). To qualify for the study, each of the 14 plants had to achieve at least 400 person-years of risk before 1978, and to be included in the cohort, a worker had to have been exposed for at least 3 months. The average year of first exposure was 1970. The cohort averaged 26.8 years of followup in the extended followup study (Steenland et al., 2004). The age at entry is not provided, nor is an age breakdown available. By the extended cutoff date on December 31, 1998, 16% of the cohort had died. Individual exposure estimates were derived for workers from 13 of the 14 plants.

The overall SMR for cancer was 0.98, based on 860 deaths (Steenland et al., 2004). The SMR for (lympho)hematopoietic cancer was 1, based on 79 cases. Exposure-response analyses, however, revealed exposure-related increases in hematopoietic cancer mortality risk, although the effect was limited to males. In categorical life-table analysis, men with >13,500 ppm-days of cumulative exposure had an SMR of 1.46, n = 13. In internal Cox regression analyses with exposure as a continuous variable, statistically significant trends in males for all hematopoietic cancer (p=0.02) and for "lymphoid" cancers (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 hematopoietic cancer (OR = 3.42; 95% CI = 1.09–10.73) and "lymphoid" cancer (OR = 3.76; 95% CI = 1.03–13.64). The exposure metrics of duration of exposure, average concentration, and maximum (8-hour time-weighted average [TWA]) concentration did not predict the hematopoietic cancer results as well as did the cumulative exposure metric.

Although the overall SMR for female breast cancer was 0.99, based on 102 deaths, the NIOSH mortality follow-up study 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; n = 13). Internal exposure-response analyses also noted a significant positive trend for breast cancer using the log of cumulative exposure and a 20-year lag time (p=0.01). In internal categorical analyses, a statistically significant OR was observed in the highest cumulative exposure quartile with a 20-year lag (OR = 3.13; 95% CI = 1.42–6.92).

In summary, although the overall external comparisons did not demonstrate increased risks, the NIOSH investigators found significant internal exposure-response relationships between exposure to EtO and cancers of the hematopoietic system, as well as breast cancer mortality. [Internal comparisons are considered superior to external comparisons in occupational epidemiology studies because internal comparisons help control for the healthy worker effect and other factors that might be more comparable within a study's worker population than between the workers and the general population.] Exposures to other chemicals in the workplace were believed to be minimal or nonexistent. This study is the most useful of the epidemiologic studies in terms of carrying out a quantitative risk assessment. It possesses 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).

It should be noted that Steenland et al. (2004) used Cox regression models, which are loglinear relative rate models, thus providing some low-dose sublinear curvature for doses expressed in terms of cumulative exposure. However, the best-fitting model for both male lymphoid and all hematopoietic cancers was for dose expressed in terms of log cumulative exposure, indicating supralinearity of the low-dose data. This is in contrast to the reported results of Kirman et al. (2004) based on the Teta et al. (1999) analysis combining the 1993 UCC leukemia data with the 1993 NIOSH leukemia data, which are claimed by the authors to provide empirical evidence supporting a quadratic dose-response relationship. The 2004 NIOSH dose-response data for hematopoietic cancers clearly do not provide empirical evidence in support of a quadratic dose-response relationship. On the contrary, the NIOSH data suggest a supralinear dose-response relationship in the observable range.

Wong and Trent (1993) investigated the same cohort as Steenland et al. (1991) but added 474 new unexplained subjects and increased the followup period by one year. They incremented the total number of deaths by 176 and added 392.2 more expected deaths. The only positive finding was a statistically significantly increased risk of NHL among men (SMR = 2.5; Obs = 16; p<0.05). However, there was a deficit risk of NHL among women. For breast cancer, there was no trend of increasing risk by duration of employment or by latency. This study has major limitations, not the least of which is a lack of detailed employment histories, making it

impossible to quantify individual exposures and develop dose-response relationships. Furthermore, the addition of more than twice as many expected deaths as observed deaths makes the analysis by the authors questionable.

In a mortality study of 1,971 male chemical workers in Italy, 637 of whom were licensed to handle EtO but not other toxic gases, Bisanti et al. (1993) reported statistically significant excesses of hematopoietic cancers (SMR = 7.1, Obs = 5, $p<0.05$). The study was limited by the lack of exposure measurements and by the young age of the cohort. Although this study suggests that exposure to EtO leads to a significant excess of hematopoietic cancer, the lack of personal exposure measurements and the fact that members were potentially exposed to other chemicals in the workplace lessen its usefulness for establishing dose-response relationships.

Hagmar et al. (1991, 1995) studied cancer incidence in 2,170 Swedish workers (861 male and 1,309 female) in two medical sterilizing plants. They determined concentrations in six job categories and estimated exposure (ppm-years) for each worker. They found hematopoietic cancers in 6 individuals versus 3.4 expected (SMR = 1.8) and a nonsignificant doubling in the risk when a 10-year latency period was considered. Even though the cohort was young, the followup time was short, and only a small fraction of the workers was highly exposed, the report is suggestive. The risk of breast cancer was less than expected (standardized incidence ratio [SIR] = 0.5, Obs = 5). In the latent category of 10 years or more, the risk was even lower (SIR = 0.4, Obs = 2).

In a large chemical manufacturing plant in Belgium (number of employees not stated), Swaen et al. (1996) performed a nested case-control study of Hodgkin's disease to determine whether a cluster of 10 cases in the active male work force was associated with any particular chemical. They found a significant association for benzene and EtO. This study is limited by the exclusion of inactive workers and the potential confounding effect of other chemicals besides EtO, and it is not useful for quantitative risk assessment.

Olsen et al. (1997) studied 1,361 male employees working at four EtO chlorohydrin process plants in the United States. Although they found a nonsignificant positive trend between duration of employment as ethylene chlorohydrin workers and hematopoietic cancer, they concluded that there was no appreciable risk in these workers, contradicting the findings of Benson and Teta (1993). The small cohort size and the lack of data on EtO exposures limit the usefulness of this study in inferring risks due to EtO.

Norman et al. (1995) studied 1,132 workers (204 male and 928 female) in a medical sterilizing plant in the United States. In the women, there was a significant excess incidence of breast cancer (SIR = 2.6, Obs = 12, $p<0.05$); no other cancer sites were elevated. The risk of breast cancer was not noted to be excessive in the few previous studies where adequate numbers of females were included and analyzed for breast cancer; however, only one of these was also an

incidence study. The followup time was too short to draw meaningful conclusions at this time. This study lacks the power to determine whether risks for cancers other than breast cancer are statistically significantly elevated. It has no information regarding historical exposure and some breast cancer victims had worked for less than one month.

Tompa et al. (1999) reported a cluster of 8 breast cancers and 8 other cancers in 98 nurses exposed to EtO in a hospital in Hungary; however, the expected number of cases cannot be identified.

The NIOSH investigators used the NIOSH cohort to conduct 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 (76% of the original cohort). Breast cancer incidence was determined from interviews (questionnaires), death certificates, and cancer registries. Interviews were obtained for 5,139 women (68% of the study cohort). The main reason for nonresponse was inability to locate the study subject (22% of cohort). The average duration of exposure for the cohort was 10.7 years. For the full study cohort, 319 incident breast cancer cases were identified, including 20 cases of carcinoma in situ. Overall, the SIR was 0.87 (0.94 excluding the in situ cases) using SEER reference rates for comparison. Results with the full cohort are expected to be underestimated, however, because of case underascertainment 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 was obtained for log cumulative exposure with a 15-year lag (p=0.05), taking age, race, and year of birth into account. Using duration of exposure, lagged 15 years, provided a slightly better fit (p=0.02), while models with maximum or average exposure did not fit as well. In the Cox regression analysis with categorical exposures and a 15-year lag, the top cumulative exposure quintile had a statistically significant OR of 1.74 (95% CI = 1.16–2.65).

In the subcohort 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 with continuous exposure variables, the model with duration of exposure (lagged 15 years) again provided the best fit (p=0.006). Both the cumulative exposure and log cumulative exposure models also 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 because of inconsistencies in exposure-response trends, possible biases due to nonresponse, 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 imprecisions in exposure estimates. Furthermore, the consistency of results between the full study cohort, which is less subject to nonresponse bias, and the subcohort with interviews, which should have full case ascertainment, alleviates some of the concerns about those potential biases.

In a study of 299 female workers employed in a hospital in Hungary where gas sterilizers were used, Kardos et al. (2003) observed 11 cancer deaths, including 3 breast cancer deaths, compared with slightly more than 4 expected total cancer deaths. Site-specific expected deaths are not available in this study, so it cannot be determined whether there is an excess risk of any site-specific cancer.

3.1.1. Conclusions Regarding the Evidence of Cancer in Humans

Most of the human studies suggest a possible 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 hematopoietic system." On the other hand, there is little strength in the magnitude of most of the estimates of risk.

The 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 positive trend is evident in the risk of lymphohematopoietic neoplasms with increasing cumulative exposure to EtO, although only in males. Despite limitations in the data, most other epidemiologic studies have also found elevated risks of lymphohematopoietic cancer from exposure to EtO. Furthermore, when the exposure is relatively pure, such as in sterilization workers, there is an elevated risk of lymphohematopoietic cancer that cannot be attributed to the presence of confounders such as those that could potentially appear in the chlorohydrin process. In addition, the studies that do not report a significant lymphohematopoietic cancer effect from exposure to EtO suffer from severe limitations, such as small numbers of cases and inadequate exposure information (see Table A-3).

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. Two 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 where exposure to EtO would be expected to have occurred among female employees, no elevated risks were seen (Hagmar et al., 1991; Hogstedt, 1988; Hogstedt et al., 1986; Coggon et al., 2004). 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.

In summary, the most compelling evidence of a cancer risk from exposure to EtO is for cancer of the lymphohematopoietic system. Increases in the risk of lymphohematopoietic cancer are present in most of the studies, manifested as an increase in either leukemia and/or cancer of the lymphoid tissue. The evidence of lymphohematopoietic cancer is strongest in the one study (the NIOSH study) that appears to possess the fewest limitations. In this large study, a significant dose-response relationship was evident with cumulative exposure to EtO. However, this effect was observed only in males and the magnitude of the effect was not large. Similarly, in most of the other studies, the increased risks are not great, and other chemicals in some of the workplaces cannot be ruled out as possible confounders. Thus, the findings of increased risks of lymphohematopoietic cancer in the NIOSH and other studies cannot conclusively be attributed to exposure to EtO. The few studies that fail to demonstrate any increased risks of cancer do not have those strengths of study design that give confidence to the reported lack of an exposure-related effect.

There is also evidence of an elevated risk of breast cancer from exposure to EtO in a few studies. The strongest evidence again comes from the NIOSH studies, which found positive exposure-response relationships for both breast cancer incidence and mortality. Hopefully, future studies will shed more light on this recent finding.

3.2. EVIDENCE OF CANCER IN EXPERIMENTAL ANIMALS

The International Agency for Research on Cancer (IARC) monograph (IARC, 1994) has summarized the rodent studies of carcinogenicity, and Health Canada (2001) has used this information to derive the levels of concern for human exposure. EPA concludes that the IARC summary of the key studies is valid and is not aware of any animal cancer bioassays that have been published since 1994. The Ethylene Oxide Industry Council (EOIC) (EOIC, 2001) also reviewed the same studies and did not cite additional studies. The qualitative results are

described here and the incidence data are tabulated in the unit risk derivation section of this document.

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 female Sprague-Dawley rats by gastric intubation twice weekly for 150 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 (8/50 and 31/50 in the low- and high-dose groups, respectively). Of the 39 tumors, 37 were squamous cell carcinomas, and metastases to other organs were common in these animals. This study was not evaluated quantitatively because oral risk estimates are beyond the scope of this document.

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 National Toxicology Program (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. Mean body weights were similar for treated and control animals, and there was no decrease in survival associated with treatment. A concentration-dependent increase in the incidence of tumors at several sites was induced in both sexes. These data are summarized in Table 1. Males had carcinomas and adenomas in the lung. Females had carcinomas and adenomas in the lung, malignant lymphomas, adenocarcinomas in the uterus, and adenocarcinomas in the mammary glands. The NTP also reports that both sexes had dose-related increased incidences of cystadenomas of the Harderian glands, but these are benign lesions and are not considered further here.

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. Mean body weights were statistically significantly decreased in both treated groups compared with controls ($p<0.05$). Increased mortality was observed in the treated groups, and the increase was statistically significant in the 100-ppm exposure group ($p<0.01$). Lynch et al. (1984) suggest that survival was affected by a pulmonary infection alone and in combination with EtO exposure. 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 (Table 2). The fact that the increased incidence of mononuclear cell leukemia was statistically significant in the low-exposure group but not in the high-exposure group is probably attributable to the increased mortality in the high-exposure

group. The increased incidence in just the terminal kill rats in the 100-ppm group was statistically significant compared with controls.

In the bioassay conducted by Snellings et al. (1984), 120 male and 120 female F344 rats in each sex and dose group were exposed to EtO via inhalation at concentrations of 0 (2 control groups of 120 rats of each sex were used), 10, 33, and 100 ppm for 6 hours per day, 5 days per week, for 2 years, with some scheduled kills at 6 (10 rats per group), 12 (10 rats per group), and 18 (20 rats per group) months. Significant decreases in mean body weight were observed in the 100-ppm exposure group in males and in the 100-ppm and 33-ppm exposure groups in females. During the 15th month of exposure, an outbreak of viral sialodacryoadenitis occurred, resulting in the deaths of 1–5 animals per group. Snellings et al. claim that it is unlikely that the viral outbreak contributed to the EtO-associated tumor findings. After the outbreak, mortality rates returned to pre-outbreak levels and were similar for all groups until the 20th or 21st month, when cumulative mortality in the 33-ppm and 100-ppm exposure groups of each sex remained above control values. By the 22nd or 23rd months, mortality was statistically significantly increased in the 100-ppm exposure groups of both sexes.

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. These data are summarized in Table 3. Note that these investigators observed the same types of tumors (splenic leukemia and peritoneal mesothelioma) seen by Lynch et al. (1982, 1984). Snellings et al. (1984) only report incidences (of incidental and nonincidental primary tumors for all exposure groups) for the 24-month (terminal) kill. However, in their paper they state that significant findings for the mononuclear cell leukemias were also obtained when all rats were included and that a mortality-adjusted trend analysis yielded positive findings for the EtO-exposed females ($p<0.005$) and males ($p<0.05$). Similarly, Snellings et al. report that when male rats with unscheduled deaths were included in the analysis of peritoneal mesotheliomas, it appeared that EtO exposure was associated with earlier tumor occurrence, and a mortality-adjusted trend analysis yielded a significant positive trend ($p<0.005$). In later publications describing brain tumors (Garman et al., 1985, 1986), both males and females had a concentration-dependent increased incidence of brain tumors (see Table 3). Garman et al. report incidences including all rats from the 18- and 24-month kills and found dead or killed moribund. The earliest brain tumors were observed in rats killed at 18 months.

3.2.1. Conclusions Regarding the Evidence of Cancer in Experimental Animals

In summary, there is strong and sufficient evidence that EtO causes cancer in experimental 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 of both epithelial origin (lung, mammary gland, uterus) and mesothelial origin (lymph tissue, blood, 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.

3.3. SUPPORTING EVIDENCE

3.3.1. Metabolism and Kinetics

Information on the kinetics and metabolism of EtO has been derived primarily from studies conducted with laboratory animals exposed via inhalation, although some limited data from humans have been identified. Details are available in several reviews (Brown et al., 1996, 1998; Csanády et al., 2000; Fennell and Brown, 2001).

Following inhalation, EtO is absorbed efficiently into the blood and rapidly distributed to all organs and tissues. EtO is metabolized primarily by two pathways (see Figure 1): (1) hydrolysis to ethylene glycol (1,2-ethanediol), with subsequent conversion to oxalic acid, formic acid, and carbon dioxide; and (2) glutathione conjugation and the formation of *S*-(2-hydroxyethyl)cysteine and N-acetylated derivatives (WHO, 2003). From the available data, the route involving conjugation with glutathione appears to predominate in mice; in larger species (including humans), the conversion of EtO is primarily via hydrolysis through ethylene glycol. Because EtO is an epoxide capable of reacting directly with cellular macromolecules, both pathways are considered to be detoxifying.

Among rodent species, there are clear quantitative differences in metabolic rates. The rate of clearance of EtO from the blood, brain, muscle, and testes was measured by Brown et al. (1996, 1998). Clearance rates were nearly identical across blood and other tissues. Following a 4-hour inhalation exposure to 100 ppm EtO in mice and rats, the average blood elimination half-lives ranged from 2.4 to 3.2 minutes in mice and 11 to 14 minutes in rats. The elimination half-life in humans is 42 minutes (Filser et al., 1992), and the half-life in salt water is 4 days (IARC, 1994).

In a more detailed study in mice, Brown et al. (1998) measured EtO concentrations in mice after 4-hour inhalation exposures at 0, 50, 100, 200, 300, or 400 ppm. They found that blood EtO concentration increased linearly with inhaled concentrations of less than 200 ppm, but above 200 ppm the blood concentration increased more rapidly than linearly. In addition, glutathione levels in liver, lung, kidney, and testes decreased as exposures increased above 200 ppm. The investigators interpreted this, along with other information, to mean that at low concentrations glutathione conjugation is responsible for the metabolism and disappearance of EtO, but at higher concentrations, when tissue glutathione begins to be depleted, the elimination

occurs via a slower non-enzymatic hydrolysis process, leading to a greater-than-linear increase in blood EtO concentration.

Fennell and Brown (2001) constructed physiologically based pharmacokinetic (PBPK) models of uptake and metabolism in mice, rats, and humans, based on previous studies. They reported that the models adequately predicted blood and tissue EtO concentrations in rats and mice, with the exception of the testes, and blood EtO concentrations in humans. Modeling 6-hour inhalation exposures yielded simulated blood peak concentrations and areas under the curve (AUCs) that are similar for mice, rats, and humans (human levels are within about 15% of rat and mouse levels; see Figure 2). In other words, exposure to a given EtO concentration in air results in similar predicted blood EtO AUCs for mice, rats, and humans.

These studies show that tissue concentrations in mice, rats, and humans exposed to a particular air concentration of EtO are approximately equal and that they are linearly related to inhalation concentration, at least in the range of exposures used in the rodent cancer bioassays (i.e., 100 ppm and below).

EtO forms DNA and hemoglobin adducts with tissues throughout the body (Walker, 1992a, b). In experiments with rats and mice exposed to EtO at concentrations of 0, 3, 10, 33, 100, or 300 (rats only) ppm for 6 hours per day, 5 days per week, for 4 weeks, Walker et al. (1992b) measured 7-(2-hydroxyethyl)guanine (HEG) in the DNA of lung, brain, kidney, spleen, liver, and testes. At 100 ppm, the adduct levels for all tissues except testis were similar (within a factor of 3), despite the fact that not all of these tissues are targets for toxicity. The study's data on the persistence of the DNA adducts indicate that DNA repair rates differ in different tissues.

In a companion paper, Walker et al. (1992a) reported measurements of hemoglobin adducts and showed how the concentration of these adducts changes according to the dynamics of red blood cell turnover. Formation of hemoglobin adducts has been used as a measure of exposure to EtO. Walker et al. (1992a) measured hemoglobin adduct formation in mice and rats exposed to 0, 3, 10, 33, 100, and 300 (rats only) ppm of EtO (6 h/day, 5 days/wk, for 4 weeks). Response was linear in both species up to 33 ppm, after which the slope significantly increased. The dose-related decrease in glutathione concentration in liver reported by Brown et al. (1998) is a plausible explanation for the higher incidence of hemoglobin adducts.

In humans, hemoglobin adducts can be used as biomarkers of recent exposure to EtO (IARC, 1994), and several studies have reported exposure-response relationships between hemoglobin adduct levels and EtO exposure levels (e.g., Schulte et al., 1992; Van Sittert et al., 1993). Hemoglobin adducts are good indicators of exposure because they are stable (DNA adducts, on the other hand, may be repaired or fixed as mutations and hence cannot be used as reliable measures of exposure). However, because levels of *N*-(2-hydroxyethyl)valine (HEVal) were approximately twofold greater in persons with a null GSTT1 genotype than in those with

positive genotypes (Yong et al., 2001), adjustments for genotype would be necessary for accuracy in inferring recent exposure from hemoglobin adduct data.

Alkylating agents may induce a dozen different DNA alkylation products (Beranek, 1990) with varying proportions, depending primarily on the electrophilic properties of the agent. The predominant DNA adduct formed by EtO and other SN2-type alkylating agents is HEG. In a study in rats, Zhao et al. (1997) reported three main adducts, HEG, 3-hydroxyethyladenine, and O-6 hydroxyethylguanine, in the ratios 200:8.8:1. In DNA extracted from the lymphocytes of unexposed individuals, mean background levels of HEG ranged from 2 to 8.5 pmol/mg DNA (Bolt, 1996). Because EtO is formed during the metabolism of ethylene, a natural body constituent, endogenous as well as exogenous sources of ethylene and EtO contribute to background alkylation of proteins such as hemoglobin and albumin as well as DNA (Bolt, 1996).

3.3.2. Mutagenicity

Since the first report of EtO induction of sex-linked recessive lethals in drosophila (Rapoport, 1948), numerous papers have been published on the positive mutagenic activity in biological systems, spanning the whole range of assay systems, from bacteriophage to higher plants and animals. Figure 3 shows the 203 test entries in the EPA Genetic Activity Profile (GAP) database. In prokaryotes and lower eukaryotes, EtO induced 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. Several publications contain details of earlier genetic toxicity studies (Thier and Bolt, 2000; Natarajan et al., 1995; Preston et al., 1995; Dellarco et al., 1990; Walker et al., 1990; Ehrenberg and Hussain, 1981). This review focuses on recently published studies that provide information on the mode of action of EtO.

3.3.2.1. *Mutations*

As a direct-acting alkylating agent, EtO has invariably yielded positive results in in vitro mutation assays from bacteriophage, bacteria, fungi, yeast, insects, plants, and mammalian cell cultures (including human cells). The results of in vivo studies on the genotoxicity of EtO have also been consistently positive following ingestion, inhalation, or injection (Tates et al., 1999). Increases in the frequency of gene mutations in the lung *(lacI* locus) (Sisk et al., 1997), in T-lymphocytes (*hprt* locus) (Walker et al., 1997), and bone marrow and testes (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).

In male Big Blue (*lacI* transgenic) B6C3F$_1$ mice exposed to 0, 50, 100, or 200 ppm (0, 92, 183, or 366 mg/m^3) EtO for 6 hours per day, 5 days per week, for 4 weeks, the observed mean frequency of mutation at the *hprt* locus in splenic T-lymphocytes was 2.2, 3.8, 6.8, and 14.1 × 10^{-6}, respectively (Sisk et al., 1997). The frequency of *hprt* mutations in splenic T-lymphocytes was increased (compared with unexposed controls) 5- to 5.6-fold in male F344 rats as well as in (nontransgenic) male B6C3F$_1$ mice exposed to 200 ppm (366 mg/m^3) EtO for 6 hours per day, 5 days per week, for 4 weeks (Walker et al., 1997). Similarly, the frequency of *lacI* mutations in the lungs, bone marrow, and spleen was increased in male Big Blue *(lacI* transgenic) B6C3F$_1$ mice exposed to 0 or 200 ppm (0 or 366 mg/m^3) EtO (Recio et al., 1999; Sisk et al., 1997).

In a later study by Recio et al. (2004), male Big Blue *(lacI* transgenic) B6C3F$_1$ mice were exposed to 0, 25, 50, 100, or 200 ppm EtO (6 hours per day, 5 days per week) for 12, 24, and 48 weeks (Recio et al., 2004). Clear mutagenic response in the bone marrow was observed only after 48 weeks, with *lacI* mutant frequencies of 7.3, 11.3, 9.3, 14.1, and 30.3 × 10^{-5}. Mutant frequencies from testes (seminiferous tubules) were significantly greater than in controls at 25, 50, and 100 ppm (48-week exposure). The *lacI* mutant frequency after 48 weeks of 200 ppm EtO exposure was not different from that of controls. The authors suggested that this was probably due to testicular toxicity. Mutation spectrum analysis of induced mutations in bone marrow indicated a decrease in mutations at G:C base pairs and an increase at A:T base pairs, exclusively in A:T→T:A transversions. The mutation spectrum in EtO-induced mutations from testes was similar to the spectrum from untreated animals. The authors suggested that the difference in mutation spectrum between the two tissues may be due to differential repair of DNA adducts.

In a study of workers in an EtO production facility (Tates et al., 1995), *hprt* mutations were measured in three exposed groups and one unexposed group (seven workers per group). No significant differences in mutant frequencies were observed between the groups; however, the authors stated that about 50 subjects per group would have been needed to detect a 50% increase.

Major et al. (2001) measured *hprt* mutations in female nurses employed in hospitals in Eger and Budapest, Hungary. This study and an earlier study measuring effects on chromosomes (see Table 4) were conducted to examine a possible causal relationship between EtO exposure and a cluster of cancers (mostly breast) in nurses exposed to EtO in the Eger hospital. The Budapest hospital was chosen because there was no apparent increase in cancer among nurses exposed to EtO. Controls were female hospital workers in the respective cities, and nurses in Eger with known cancers were excluded. Mean peak levels of EtO were 5 mg/m^3 (2.7 ppm) in Budapest and 10 mg/m^3 (5.4 ppm) in Eger. *Hprt* variant frequencies in both controls and EtO-exposed workers in the Eger hospital were higher than either group in the Budapest hospital, but there was no significant increase among the EtO-exposed workers in either hospital when

compared with the respective controls. The authors noted that the *hprt* variant frequencies among smoking EtO-exposed nurses in Eger were significantly higher than among smokers in the Eger controls; however, the fact that the *hprt* variant frequency was almost three times higher in nonsmokers than in smokers in the Eger hospital control group raises questions about the basis of the claimed EtO effect.

3.3.2.2. *Sister Chromatid Exchanges*

The genotoxicity of EtO was demonstrated in humans as early as 1979. Table 4 summarizes the cytogenetic effects of EtO on human exposures. Garry et al. (1979) analyzed SCEs in lymphocytes cultured from exposed individuals as well as comparable controls. Significant increase in SCE was observed at three weeks and at eight weeks following exposure to EtO. Although this study does not describe the exact exposure estimates, EtO was recognized as a mutagenic or genotoxic agent.

SCE frequency in workers exposed to high levels of EtO in a hospital sterilization service was studied by Laurent et al. (1984). Blood samples were obtained retrospectively from a group of 25 subjects exposed to high levels of EtO for a period of two years. A significant increase in SCE rate was observed in the exposed group when compared with the control group. The authors concluded that the effect of exposure to EtO was sufficient to produce a cumulative—and in some cases a persistent—genetic change.

Peripheral blood lymphocytes of nurses exposed to low and high doses of EtO were studied by Major et al. (1996). SCEs were slightly elevated in the low-dose exposure group but were significantly increased in the high-dose exposure group. Several studies by Sarto et al. (1984, 1987, 1990, 1991) showed significant increases in chromosomal aberrations, SCEs, and micronucleus formation (Table 4).

3.3.2.3. *Chromosomal Aberrations*

Clare et al. (1985) conducted chromosomal analysis on lymphocytes from 33 workers employed in the manufacture of EtO. A slightly higher frequency of chromatid aberrations was observed in the cells of the EtO workers than in those of controls. Further, a positive correlation between length of employment in the EtO group and the number of aberrations was observed (Table 4). Galloway et al. (1986) studied chromosomal aberration frequencies in 61 employees potentially exposed to EtO. Three work sites with different historical ambient levels of EtO were chosen for study. Blood samples were drawn several times over a 24-month period and aberrations were analyzed in 100 cells per sample after culture for 48–51hours. At work sites I and II, no consistent differences in aberration frequencies were found. However, at work site III, aberration frequencies in potentially exposed individuals were significantly increased when

compared with controls. A previous study by the same group (Stolley et al., 1984) showed an association between SCE frequency and EtO exposure. When the aberrations were compared with the levels of SCEs, the authors found a weak overall association (Table 4).

Further, Lerda and Rizzi (1992) showed a significant increase in chromosomal aberration frequencies in EtO-exposed individuals when compared with controls. Major et al. (1996) studied hospital nurses exposed to low doses and high doses of EtO for changes in structural and numerical chromosomal aberrations. Chromosomal aberrations were found to be significantly elevated in both the low-dose and the high-dose exposure groups. Deletions—and to a lesser extent, chromatid exchanges and dicentrics—were detected in the low-dose exposure group; however, in the high-dose group, in addition to the increased number of deletions, the frequencies of dicentrics and rings showed a significant excess when compared with controls. The authors acknowledged that an unexpected, significant increase in dicentrics and ring frequencies was detected among the controls. When analyzed for confounding factors, a possible active confounding factor was natural radioactivity from the local tap water. Several other studies by Sarto et al. (1984, 1987, 1990, 1991) showed significant increase in chromosomal aberrations after exposure to EtO. In a study of 28 EtO-exposed sterilizer workers and 20 unexposed controls, Hogstedt et al. (1983) reported a statistically significant increase in micronuclei, but not chromosomal breaks or gaps, in bone marrow cells (erythroblasts and polychromatic erythrocytes) in the exposed workers, adjusted for age, smoking, drug intake, and exposure to ionizing radiation.

The above data clearly indicate that EtO is a genotoxic agent that causes a variety of types of genetic damage.

As discussed by Preston (1999), a variety of cytogenetic assays can be used to measure induced chromosome damage. However, most of the assays commonly employed measure events that are detectable only in the first (or in some cases the second) metaphase after exposure and require DNA synthesis to convert DNA damage into a chromosomal aberration. In addition, DNA repair is operating in peripheral lymphocytes to repair induced DNA damage. The events measured include all types of chromosomal aberrations, micronuclei, SCE, and numerical chromosomal changes. Thus, for acute exposures, the timing of sampling is of great importance. For chronic studies, the endpoints measure only the most recent exposures, and if the time between last exposure and sampling is long, any induced DNA damage not converted to a stable genotoxic alteration is certain to be missed. Stable chromosomal aberrations include reciprocal translocations, inversions, and some fraction of insertions and deletions as well as some numerical changes. However, until the development of fluorescent in situ hybridization (FISH), chromosome banding techniques were needed to detect these types of aberrations.

Preston (1999) has provided an exhaustive review of the cytogenetic effects of EtO. Table 4 shows the details of the studies that were reviewed. In addition to summarizing the available cytogenetic studies of exposed workers, Preston discussed the basic guidelines for cytogenetic assays, noting especially that because most cytogenetic assays measure damage that is either repaired rapidly or is nontransmissible, they are not valuable in chronic exposures in either laboratory animals or humans. The situation in humans is further confounded because of the dependence of chromosomal aberrations on age, smoking status, medical condition (including radiation exposure), and other life style variables. Based on the review, Preston (1999) concluded that high exposures to EtO can be detected as increases in unstable chromosomal aberrations or SCE in peripheral lymphocytes but that chronic or low-level acute exposures are not detectable using routine measures.

The overall available data from in vitro studies, animal models, and epidemiological studies indicate that EtO is both a mutagen and a genotoxicant. It has been recognized that stable translocations seen in human leukemias can arise from similar DNA adducts that produce chromosome breaks, micronuclei, SCEs, and even gene mutations observed in peripheral lymphocytes.

3.4. MODE OF ACTION

EtO is an alkylating agent that has consistently been found to produce numerous genotoxic effects in a variety of biological systems ranging from bacteriophage to occupationally exposed humans. It is carcinogenic in mice and rats, inducing tumors of the lymphohematopoietic system, brain, lung, connective tissues, uterus, and mammary gland. In addition, epidemiological studies have shown an increased risk of various types of human cancers (Table A-5), in particular lymphohematopoietic and breast cancers. Target tissues for EtO carcinogenicity in laboratory animals are both epithelial and mesothelial in origin and are not clearly attributable to any specific type of genetic alteration. The lymphomas in mice induced by EtO are considered to be generally similar in characteristics to leukemias in humans (U.S. EPA, 1997). Although the precise mechanism(s) by which the multi-site carcinogenicity in mice, rats, and humans occurs cannot be well established, currently available information indicates that genotoxicity plays an important role in EtO-induced carcinogenicity.

Exposure of cells to DNA-reactive agents results in the formation of carcinogen-DNA adducts. The formation of DNA adducts results from a sequence of events involving absorption of the agent, distribution to different tissues, and accessibility of the molecular target (Swenberg et al., 1990). Alkylating agents may induce several different DNA alkylation products (Beranek, 1990) with varying proportions, depending primarily on the electrophilic properties of the agent. The predominant DNA adduct formed by EtO is HEG. Zhao et al. (1997) reported three main

adducts in rat liver and lymphocytes: HEG, 3-hydroxyethyladenine, and O-6 hydroxyethylguanine in the ratios 200:8.8:1. The various adducts are processed by different repair pathways, and the subsequent genotoxic response elicited by unrepaired DNA adducts is dependent on a wide range of variables. HEG adducts result in various types of cytogenetic damage, including gene mutations, which have been observed in exposed mice and rats. The predominant fraction of mutations detected by sequencing were base pair changes that involved adenine as well as guanine adducts (Walker and Skopek, 1993; Walker et al., 1999; Recio et al., 2004). Further, DNA adducts, SCEs, and *hprt* mutations resulting from EtO exposure in rats have shown statistically significant linear dose-response functions (van Sittert et al., 2000).

The events involved in the formation of chromosome damage from HEG are complex. N–alklylated bases are removed from DNA by base excision repair pathways. A review by Memisoglu and Samson (2000) notes that the action of DNA glycosylase and apurinic endonuclease creates a DNA single-strand break, which can in turn lead to DNA double-strand breaks (DSBs). DSBs can also be produced by normal cellular functions, such as during V(D)J recombination in the development of lymphoid cells or topoisomerase II-mediated cleavage at defined sites. A recent review of mechanisms of DSB repair indicates that the molecular mechanisms are not fully understood (Pfeiffer et al., 2000). This review provides a thorough discussion of both sources (endogenous and exogenous) of DSBs and the variety of repair pathways that have evolved to process the breaks. Although homology-directed repair generally restores the original sequence, during nonhomologous end-joining (NHEJ), the ends of the breaks are frequently modified by addition or deletion of nucleotides.

Leukemias, like all other cancers, are believed to be a consequence of an accumulation of genetic and epigenetic changes involving multiple genes and chromosomal alterations. Although it is clear that chromosome translocations are common features of hematopoietic cancers, there is evidence that mutations in p53 or N–*ras* are involved in some types of leukemia (U.S. EPA, 1997). It should also be noted that therapy-related leukemias exhibiting reciprocal translocations are generally seen in patients who have previously been treated with chemotherapeutic agents that act as topoisomerase II inhibitors (U.S. EPA, 1997). In NHL, the BCL6 gene is frequently activated by translocation with breakpoints within the gene (Chaganti et al., 1998) as well as by mutations within the gene coding sequence (Lossos and Levy, 2000). Preudhomme et al. (2000) observed point mutations in the AML1 gene in 9 of 22 patients with the Mo type of acute myeloid leukemia (AML), and Harada et al. (2003) identified AML1 point mutations in cases of radiation-associated and therapy-related myelodysplastic syndrome/AML. In both reports, point mutations within the coding sequence were found in patients with normal karyotypes as well as some with translocations or other chromosomal abnormalities. Several models have been developed to integrate these various types of genetic alterations. One recent model suggests that

two general types of therapy-related AML can be subdivided into at least eight genetic pathways that have different etiologies and different biologic characteristics (Pedersen-Bjergaard et al., 2002).

A mode-of-action-motivated modeling approach based solely on chromosome translocations has been proposed by Kirman et al. (2004). The authors suggested a nonlinear dose-response for EtO and leukemia, based on a consideration that "chromosomal aberrations are the characteristic initiating events in chemically induced acute leukemia and gene mutations are not characteristic initiating events." They thus proposed that EtO must be responsible for two nearly simultaneous DNA adducts, yielding a dose-squared relationship between EtO exposure and leukemia risk. However, as discussed above, there is evidence that does not support the assumption that chromosomal aberrations represent the sole initiating event. In fact, these aberrations or translocations could be a downstream event resulting from genomic instability. In addition, if two reactions with DNA resulting in chromosomal aberrations or translocations are early-occurring events in some EtO-induced lymphohematopoietic cancers, it is not necessary that both events be associated with EtO exposure (e.g., background error repair rates or exposure to other alkylating agents may be the cause). Furthermore, EtO could also produce translocations indirectly by forming DNA or protein adducts that affect the normally-occurring recombination activities of lymphocytes or the repair of spontaneous double-strand breaks.

Of course, with chronic exposure, the observed stable translocations are the combined effect of induced translocations and their persistence. Clearly, with respect to leukemia related to EtO exposure, the accumulations of translocations may be of mechanistic relevance. Dose-response curves for translocation frequencies following protracted or chronic radiation exposure have shown significant linear but not quadratic terms in experimental studies in mice (Sorensen et al., 2000). Tucker et al. (1997) reported translocation frequencies linear with dose (the quadratic coefficient was negative) among 81 radiation workers at the Sellafield Nuclear Facility.

In summary, EtO induces a variety of types of genetic damage. It directly interacts with DNA, resulting in gene mutations and chromosome damage. Depending on a number of variables, the predominant DNA adduct (HEG) (1) may be repaired, (2) may result in a base-pair mutation during replication, or (3) may be converted to a DSB, which also may be repaired or result in unstable (micronuclei) or stable (translocation) cytogenetic damage. All of the available data are strongly supportive of a mutagenic mode of action involving gene mutations and chromosomal aberrations (translocations, deletions, or inversions) that critically alter the function of oncogenes or tumor suppressor genes. Although it is clear that chromosome translocations are common features of many hematopoietic cancers, there is evidence that mutations in p53, AML1 or N–*ras* are involved in other leukemias. The current scientific consensus is that there is very good correspondence between ability of an agent to cause mutations, as does EtO, and

carcinogenicity. All of the above scientific evidence points to a mutagenic mode of action with linear dose response functions, and therefore, application of linearity of the dose-response relationship seems appropriate.

3.4.1. Analysis of the Mode of Action for Ethylene Oxide Carcinogenicity Under EPA's Mode of Action Framework

In this section, the mode of action evidence for EtO carcinogenicity is analyzed under the mode of action framework in EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a, Section 2.4.3).

The *hypothesis* is that EtO carcinogenicity has a mutagenic mode of action. This hypothesized mode of action is presumed to apply to all of the tumor types.

The *key events* in the hypothesized 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 translocations, which can also result in mutations at the translocation sites. Mutagenicity is a well-established cause of carcinogenicity.

1. *Is the hypothesized mode of action sufficiently supported in the test animals?*

Numerous studies have demonstrated that EtO forms protein and DNA adducts, in mice and rats (see Sections 3.3.1 and 3.4 and Figure 2). For example, Walker et al. (1992a, b) demonstrated that EtO forms protein adducts with hemoglobin in the blood and DNA adducts with tissues throughout the body, including in the lung, brain, kidney, spleen, liver, and testes.

In addition, there is incontrovertible evidence that EtO is mutagenic (see Section 3.2.2). The evidence is *strong* and *consistent*; EtO has invariably yielded positive results in in vitro mutation assays from bacteriophage, bacteria, fungi, yeast, insects, plants, and mammalian cell cultures. The results of in vivo studies on the mutagenicity and genotoxicity of EtO have also been consistently positive following ingestion, inhalation, or injection. Increases in the frequency of gene mutations in the lung, in T-lymphocytes, in bone marrow, and in testes have been observed in transgenic mice exposed to EtO via inhalation at concentrations similar to those in the mouse carcinogenesis bioassays.

Ethylene oxide induces a variety of mutagenic and genotoxic effects, including chromosome breaks, micronuclei, SCEs, and gene mutations; however, the more general effect of mutagenicity/genotoxicity is *specific* and occurs in the absence of cytotoxicity or other overt toxicity. A *temporal relationship* is also clearly evident, with adducts and mutagenicity observed in subchronic assays.

Dose-response relationships have been observed between EtO exposure in vivo and hemoglobin adducts (e.g., Walker et al., 1992a), as well as DNA adducts, SCEs, and *hprt* mutations (e.g., van Sittert et al., 2000) (see also Sections 3.3 and 3.4). A mutagenic mode of action for EtO carcinogenicity also clearly comports with notions of *biological plausibility* and *coherence* because EtO is a direct-acting alkylating agent. Such agents are generally capable of forming DNA adducts, which in turn have the potential to cause genetic damage, including mutations; and mutagenicity, in its turn, is a well-established cause of carcinogenicity. This chain of key events is consistent with current understanding of the biology of cancer.

In addition to the clear evidence supporting a mutagenic mode of action in test animals, we are not aware of any alternative or additional hypothesized modes of action for EtO carcinogenicity.

2. *Is the hypothesized mode of action relevant to humans?*

The evidence discussed above demonstrates that EtO is a systemic mutagen in test animals; thus, there is the presumption that it would also be a mutagen in humans. Moreover, there is human evidence directly supporting a mutagenic mode of action for EtO carcinogenicity. Several studies of humans have reported exposure-response relationships between hemoglobin adduct levels and EtO exposure levels (e.g., Schulte et al., 1992; van Sittert et al., 1993; see Section 3.3.1), demonstrating the ability of EtO to bind covalently in systemic human cells, as it does in rodent cells.

In addition, EtO has yielded positive results in in vitro mutagenicity studies of human cells (see Figure 2). There is also clear evidence from a number of human studies that EtO causes chromosomal aberrations, SCEs, and micronucleus formation in peripheral blood lymphocytes (see Sections 3.3.2.2 and 3.3.2.3 and Table 4). At least one study suggested an exposure-response relationship for the formation of SCEs in peripheral blood lymphocytes (Major et al., 1996). Another study reported a statistically significant increase in micronuclei in bone marrow cells in EtO-exposed workers (Hogstedt et al., 1983).

Finally, there is strong evidence that EtO causes cancer in humans, including cancer types observed in rodent studies (i.e., lymphohematopoietic cancers and breast cancer), providing further weight to the relevance of the aforementioned events to the development of cancer in humans (see Sections 3.1 and 3.5.1).

In conclusion, the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity.

3. *Which populations or lifestages can be particularly susceptible to the hypothesized mode of action?*

The mutagenic mode of action is considered relevant to all populations and lifestages. According to EPA's Supplemental Guidance (U.S. EPA, 2005b), there may be increased susceptibility to early-life exposures for carcinogens with a mutagenic mode of action. Therefore, 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, increased early-life susceptibility should be assumed and, if there is early-life exposure, the age-dependent adjustment factors (ADAFs) should be applied, in accordance with the Supplemental Guidance.

In addition, as discussed in Section 3.5.2, people with DNA repair deficiencies or genetic polymorphisms conveying a decreased efficiency in detoxifying enzymes may have increased susceptibility to EtO carcinogenicity.

3.5. HAZARD CHARACTERIZATION

3.5.1. Characterization of Cancer Hazard

In humans there is evidence that EtO exposure may be causally associated with lymphohematopoietic cancer, but the evidence is not strong enough to be conclusive. The strongest evidence comes from a high-quality study of a large NIOSH cohort. Of the seven relevant Hill criteria for causality (Hill, 1965), *temporality*, *coherence*, and *biological plausibility* are largely satisfied. There is evidence of *consistency* between studies with respect to cancer of the lymphohematopoietic system as a whole. There is some evidence of a dose-response relationship (*biological gradient*) in males but not in females. There is little *strength* in the magnitude of most of the risk estimates.

Most of the relevant studies focus on examining risks of cancer associated with subcategories of the lymphohematopoietic organ system. These cancers include leukemia and its various forms (i.e., myeloid or lymphocytic) and also Hodgkin's disease, NHL, reticulosarcoma, and myeloma. One study has focused on "lymphoid cancer," which is a combination of lymphocytic leukemia, NHL, and myeloma. No other study has examined the risk of this particular combination. In this study, risk of cancer of the lymphoid tissue was significantly elevated in subgroups of the workforce likely to have received the highest exposures to EtO. Elevated risks of other subcategories of the hematopoietic system—either singly or in combination—have sometimes, but not always, appeared in other studies.

In most of these studies, when all the subcategories are combined, an enhanced risk of cancer of the lymphohematopoietic system is evident, and in some studies, it is significant. Hence there is some *specificity* with respect to the lymphohematopoietic system, but the *specificity*

criterion is not expected to be satisfied by agents, such as EtO, that are not only widely distributed in all tissues but are also directly acting chemicals.

There is also recent evidence of an increased breast cancer risk in females from exposure to EtO. This evidence comes predominantly from high-quality studies of the large NIOSH cohort, in which positive exposure-response relationships for both breast cancer incidence and mortality were observed. The criteria of temporality, coherence, and biological plausibility are also satisfied. On the other hand, the magnitudes of the risk were not large, and none of the other studies had enough breast cancer cases to be very informative.

Stomach cancer was noted in the earlier Hogstedt studies but is not found in recent studies. Pancreatic cancer was observed in some studies and not others, and some studies observed no EtO-related cancer risks.

The experimental animal evidence for carcinogenicity is concluded to be "sufficient" based on findings of tumors at multiple sites, by both oral and inhalation routes of exposure, and in both sexes of both rats and mice. Tumor types resulting from inhalation exposure included mononuclear cell leukemia in male and female rats and malignant lymphoma and mammary carcinoma in female mice, suggesting some site concordance with the lymphohematopoietic and breast cancers observed in humans, also exposed by inhalation.

The evidence of genotoxicity is very strong, and there is no doubt that EtO is mutagenic. EtO is a direct-acting alkylating agent and has invariably tested positive in in vitro mutation assays from bacteriophage, bacteria, fungi, yeast, insects, plants, and mammalian cell cultures (including human cells). In mammalian cells, EtO-induced genotoxic effects include unscheduled DNA synthesis, gene mutations, SCEs, micronuclei, and chromosomal aberrations. The results of in vivo genotoxicity studies of EtO have also been consistently positive following ingestion, inhalation, or injection. Increases in frequencies of gene mutations have been reported in the lung, T-lymphocytes, bone marrow, and testes. Several studies of humans occupationally exposed to EtO have reported increased levels of SCEs, chromosomal aberrations, and micronuclei in lymphocytes of exposed workers, and one study has reported increased levels of micronuclei in bone marrow cells (erythroblasts and polychromatic erythrocytes) in EtO-exposed workers. In addition to the various genotoxic effects of EtO, it is well established that EtO induces hemoglobin adducts in rodents and in humans.

In the framework of EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the statement can be made that EtO is carcinogenic to humans because the evidence satisfies the conditions required in the absence of conclusive epidemiologic evidence establishing cause and effect: (1) there is evidence of cancer in humans associated with EtO exposure—strong evidence for lymphohematopoietic cancers and some evidence for breast cancer in EtO-exposed workers—although less than conclusive; (2) there is extensive evidence of EtO-induced

carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice; (3) EtO is a direct-acting alkylating agent whose mutagenic and genotoxic capabilities have been well established in a variety of experimental systems, and the mode of carcinogenic action in animals involves the key event of DNA adduct formation, which may result in mutation, chromosome breaks, or chromosome translocation; and (4) chromosome damage, including chromosomal aberrations, SCEs, and micronuclei, has been observed in human populations exposed to EtO. EtO is regarded as carcinogenic via the oral route as well as by inhalation (where nearly all of the evidence has accumulated) because it causes tumors in laboratory animals by both routes of exposure and the mode of action of EtO is independent of the route of exposure.

3.5.2. Susceptible Lifestages and Subpopulations

There are no data on the relative susceptibility of children and the elderly when compared with adult workers, in whom the evidence of hazard has been gathered, but because EtO does not have to be metabolized before binding to DNA and proteins, the maturing of enzyme systems in very young children is thought not to be a predominant factor in its hazard, at least for activation. However, the immaturity of *detoxifying* enzymes in very young children may increase children's susceptibility because they may clear EtO at a slower rate than adults. As discussed in Section 3.3.1, EtO is metabolized (i.e., detoxified) primarily by hydrolysis in humans but also by glutathione conjugation. Both hydrolytic activity and glutathione-S-transferase activity apparently develop after birth (Clewell et al., 2002); thus, very young children might have a decreased capacity to detoxify EtO compared to adults.

People with DNA repair deficiencies such as xeroderma pigmentosum, Bloom's syndrome, Fanconi anemia, and ataxia telangiectasia (Gelehrter and Collins, 1990) are expected to be especially sensitive to the damaging effects of EtO exposure. Paz-y-Mino et al. (2002) have recently identified a specific polymorphism in the excision repair pathway gene *hMSH2*. The polymorphism was present in 7.5% of normal individuals and in 22.7% of NHL patients, suggesting that this polymorphism may be associated with an increased risk of developing NHL. In addition, Yong et al. (2001) measured approximately twofold greater EtO-hemoglobin adduct levels in occupationally exposed persons with a null GSTT1 genotype than in those with positive genotypes.

3.5.3. Cancer Classification Conclusions of Other Agencies

Organizations other than EPA have come to similar conclusions regarding the carcinogenicity of EtO. Health Canada (2001) concluded that "EtO is highly likely to be carcinogenic in humans, based on consideration of cytogenetic changes in people with

occupational exposures and overwhelming evidence of the biological plausibility of its carcinogenicity, which is based on animal carcinogenesis bioassays and convincing evidence of genotoxicity in all systems tested. This evidence adds to the less-than-convincing evidence of carcinogenicity in human studies." The World Health Organization's Concise International Chemical Assessment Document (CICAD) on EtO, which is based largely on Health Canada's material, reached the same conclusion that EtO is "highly likely to be carcinogenic to humans" (WHO, 2003). Similarly, in its ninth report on carcinogens, the National Toxicology Program (NTP, 2000) has placed EtO in the category "known to be a human carcinogen." The EOIC (2001), using the descriptors in EPA's 1999 proposed carcinogen risk assessment guidelines (U.S. EPA, 1999), concluded that EtO is "likely to be carcinogenic" to humans, a classification that implies more uncertainty than the highest-degree-of-evidence category of "carcinogenic" to humans. IARC (1994) concluded that EtO is carcinogenic to humans and assigned it to its Group 1 category.

4. CANCER DOSE-RESPONSE RELATIONSHIP FOR INHALATION EXPOSURE

4.1. INHALATION UNIT RISK ESTIMATES DERIVED FROM HUMAN DATA

The NIOSH retrospective cohort study of more than 18,000 workers in 13 sterilizing facilities (Steenland et al., 2003, 2004) provides the most appropriate data sets for deriving quantitative cancer risk estimates in humans for several reasons: (1) exposure estimates were derived for the individual workers, (2) the cohort was large and diverse (e.g., 55% female), and (3) there was little reported exposure to chemicals other than EtO. The early exposures for which no measurements were available were determined by consultations with plant industrial hygienists and the use of regression modeling to estimate exposures to each individual as a function of facility, exposure category, and time period. The investigators were then able to estimate the cumulative exposure (ppm × days) for each individual worker by multiplying the estimated exposure for each job (exposure category) held by the worker by the number of days spent in that job and summing over all the jobs held by the worker. Steenland et al. (2004) present followup results for the cohort mortality study previously discussed by Steenland et al. (1991) and Stayner et al. (1993). Positive findings in the current followup include increased rates of (lympho)hematopoietic cancer mortality in males and of breast cancer mortality in females. Steenland et al. (2003) present results of a breast cancer incidence study of a subcohort of 7,576 women from the NIOSH cohort.

The other major occupational study (Teta et al., 1993) described risks in a single EtO-manufacturing facility, but this study is less useful for estimating quantitative cancer risks for a

number of reasons. Because of the more indirect method of determining exposures (inferring exposure to the West Virginia cohort from other, possibly dissimilar, plants in Texas and Minnesota), the resulting estimates of individual exposure are less reliable. Furthermore, this cohort is of smaller size, and there is the possibility of co-exposure to other chemicals, such as ethylene dichloride.

The derivation of unit risk estimates, defined as the lifetime risk of cancer from chronic inhalation of EtO per unit of air concentration, for lymphohematopoietic cancer mortality and incidence in males and for breast cancer mortality and incidence in females, based on results of the recent analyses of the NIOSH cohort, is presented in the following subsections.

4.1.1. Risk Estimates for Lymphohematopoietic Cancer

4.1.1.1. *Lymphohematopoietic Cancer Results From the NIOSH Study*

Steenland et al. (2004) investigated the relationship between EtO exposure and mortality from cancer at a number of sites using life-table analyses with the U.S. population as the comparison population. Categorical analyses were also done by quartiles of cumulative exposure. Then, to further investigate apparent exposure-response relationships observed for (lympho)hematopoietic cancer and breast cancer, internal exposure-response analyses were conducted using Cox proportional hazards models, which have the form

$$\text{Relative rate (RR)} = e^{\beta X},$$

where β represents the regression coefficient and X is the exposure. A nested case-control approach was used, with age as the time variable used to form the risk sets. Risk sets were constructed with 100 controls randomly selected for each case from the pool of those surviving to at least the age of the index case. According to the authors, use of 100 controls per case has been shown to result in ORs virtually identical to the RR estimates obtained with full cohorts. Cases and controls were matched on race (white/nonwhite), sex, and date of birth (within 5 years). Exposure was the only covariate in the model, so the *p* value for the model also serves as a *p* value for the regression coefficient, β, as well as for a test of exposure-response trend.

The exposure-response analyses focused on cumulative exposure and (natural) log cumulative exposure, with various lag periods. A lag period defines an interval before death, or end of followup, during which any exposure is disregarded because it is not considered relevant to the outcome under investigation. One ppm × day was added to cumulative exposures in lagged analyses to avoid taking the log of 0. Steenland et al. found that, for all lymphohematopoietic cancers combined, positive exposure-response trends were seen only in males. Some of the results for males are presented in Table 5. Steenland et al. also analyzed a subcategory of

lymphohematopoietic cancers that they called "lymphoid" cancers; these included NHL, myeloma, and lymphocytic leukemia. Positive trends were also observed for these cancers, again concentrated in males, but the model fits were not notably better than for all lymphohematopoietic cancers, and the "lymphoid" category did not include Hodgkin's lymphoma, which also exhibited evidence of exposure-response trends, although based on few cases. In addition, misclassification or nonclassification of tumor type is more likely to occur for subcategories of lymphohematopoietic cancer (e.g., 4 of the 25 leukemias in the analyses were classified as "not specified"). Finally, the exposure-response modeling results for lymphohematopoietic cancer are based on more cases (37 deaths in males) than are the results for "lymphoid" cancer (n = 27). Risk estimates based on "lymphoid" cancer results are presented for comparison. Although myeloid and lymphoid cells develop from different progenitor cells, these progenitor cells derive from the same pluripotent stem cells. Thus, without a clearer reason for subcategorizing the lymphohematopoietic cancers and given the misclassification issues and the smaller numbers of cases in the "lymphoid" category, risk estimates based on the more comprehensive results for all lymphohematopoietic cancers are preferred in this assessment. Other EtO exposure metrics (duration of exposure, average exposure, and peak exposure) were also examined, but models using these metrics did not generally predict lymphohematopoietic cancer as well as models using cumulative exposure. For additional details and discussion of the Steenland et al. (2004) study, see Appendix A.

4.1.1.2. *Prediction of Lifetime Extra Risk of Lymphohematopoietic Cancer Mortality*

The results of internal exposure-response analyses of lymphohematopoietic cancer presented by Steenland et al. (2004) and summarized in Table 5 were used for predicting the extra risks of lymphohematopoietic cancer mortality in males from continuous environmental exposure to EtO. Extra risk is defined as

$$\text{Extra risk} = (Rx-Ro)/(1-Ro),$$

where Rx is the lifetime risk in the exposed population and Ro is the lifetime risk in an unexposed population (i.e., the background risk). These risk estimates were calculated using the β regression coefficients and an actuarial program that accounts for competing causes of death.[1]

[1]This program is an adaptation of the approach previously used by the Committee on the Biological Effects of Ionizing Radiation (BEIR, 1988). The same methodology was also used in EPA's 1,3-butadiene health risk assessment (U.S. EPA, 2002). A spreadsheet illustrating the extra risk calculation for the derivation of the LEC_{01} for lymphohematopoietic cancer incidence in males (see Section 4.1.1.3) is presented in Appendix C.

U.S. age-specific all-cause mortality rates for 1999 for males of all race groups combined (NCHS, 2002) were used to specify the all-cause background mortality rates in the actuarial program. The National Center for Health Statistics 1997–2001 cause-specific background mortality rates for all lymphohematopoietic cancers in males were obtained from a Surveillance, Epidemiology, and End Results (SEER) report (NCI, 2004a). The risks were computed up to age 85 for continuous exposures to EtO. Conversions between occupational EtO exposures and continuous environmental exposures were made to account for differences in the number of days exposed per year (240 vs. 365 days) and in the amount of air inhaled per day (10 vs. 20 m^3; U.S. EPA, 1994). An adjustment was also made for the lag period. The reported standard errors for the regression coefficients from Table 5 and from the weighted linear regression calculation described below were used to compute the 95% upper confidence limits (UCLs) for the relative rates, based on a normal approximation.

The best-fitting model presented by Steenland et al. (2004) for all lymphohematopoietic cancer mortality in males was for log cumulative exposure with a 15-year lag (p=0.02). However, using the log cumulative exposure model to estimate the risks from low environmental exposures is problematic because this model, which is intended to fit the full range of occupational exposures in the study, is highly supralinear (i.e., risk increases steeply with increasing exposures in the low exposure range and then plateaus), and results are unstable for low exposures (i.e., small changes in exposure correspond to large changes in risk; see Figure 4). Consideration was thus given to the cumulative exposure model (p=0.12), which is typically used and which is stable at low exposures. However, the Cox regression model with cumulative exposure is sublinear for low exposures and does not reflect the apparent supralinearity of the data.

It was determined that the best way to reflect the data in the lower exposure region, which is the region of interest for low-exposure extrapolation, was to do a weighted linear regression of the results from the model with categorical cumulative exposure and a 15-year lag. In addition, the highest exposure group was not included in the regression to alleviate some of the "plateauing" in the exposure-response relationship at higher exposure levels and to provide a better fit to the lower exposure data. (Linear modeling of categorical epidemiologic data and elimination of the highest exposure group(s) to obtain a better fit of low-exposure data are both standard techniques used in EPA risk assessments [U.S. EPA, 2005a].) The weights used for the ORs were the inverses of the variances, which were calculated from the confidence intervals. Mean and median exposures for the cumulative exposure groups were kindly provided by Dr. Steenland (e-mail dated April 21, 2004, from Kyle Steenland, Emory University, to Jennifer Jinot,

U.S. EPA).[2] The mean values were used for the weighted linear regression because the (arithmetic) mean exposures best represent the model's linear relationship between exposure and cancer risk. If the median values had been used, a slightly larger regression coefficient would have been obtained, resulting in slightly larger risk estimates.

Using this approach,[3] a regression coefficient of 0.000347 per ppm × day (SE = 0.000251 per ppm × day) was obtained from the weighted linear regression of the categorical results. These parameter estimates were used as the basis for the primary risk calculations for lymphohematopoietic cancer in males. Risk estimates using the model results for the continuous exposure variables (i.e., cumulative exposure and log cumulative exposure; see Table 5) are also derived for comparison.

Point estimates and one-sided 95% UCLs for the extra risk of all lymphohematopoietic cancer mortality in males associated with varying levels of environmental exposure to EtO based on the Steenland et al. (2004) model results were determined by the actuarial program; the results are presented in Table 6 (point estimates only are presented from the continuous variable comparison models). The models based on cumulative exposure yield extra risk estimates that are fairly linear for exposures below about 0.1 to 1 ppm but not above 1 ppm. The risk estimates based on log cumulative exposure, on the other hand, are not (low-dose) linear even in the range of 0.0001 to 0.001 ppm, the lowest exposure concentrations evaluated (i.e., not linear with respect to low-exposure extrapolation to zero exposure).

Consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the same data and methodology were also used to estimate the exposure level (EC_x; "effective concentration") and the associated 95% lower confidence limit (LEC_x) corresponding to an extra risk of 1% (x = 0.01). A 1% extra risk level is commonly used for the determination of the point of departure (POD) for low-dose extrapolation from epidemiological data; higher extra risk levels, such as 10%, would be an upward extrapolation for these data. Based on the actuarial program, the risk ratio (i.e., Rx/Ro) for an extra risk of 1% for all lymphohematopoietic cancers is 1.5, which better corresponds with the ORs reported by Steenland et al. (2004) than the higher risk ratio of 5.9 that would be associated with a 10% extra risk. Thus, 1% extra risk was selected for determination of the POD, and, consistent with the *Guidelines for Carcinogen Risk Assessment*, the LEC value corresponding to that risk level was used as the actual POD. For the linear model

[2]Mean exposures for males with a 15-year lag for the exposure categories in Table 5 were 442, 2,191, 7,105, and 60,269 ppm × days. Median values were 360, 2,093, 6,230, and 43,212 ppm × days. These values are for the risk sets but should provide a good approximation to the full cohort values.

[3]Equations for this weighted linear regression approach are presented in Rothman (1986), pp. 343–344.

that was selected, the unit risk is independent of the benchmark risk level used to determine the POD; however, selection of a benchmark risk level is useful for comparisons across models.

Because EtO is clearly mutagenic, a linear low-dose extrapolation was performed, also in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The EC_{01}, LEC_{01}, and inhalation unit risk estimates for the different lymphohematopoietic cancer mortality models examined are presented in Table 7. As discussed above, the unit risk estimate based on linear regression of the Steenland et al. categorical results using cumulative exposure with a 15-year lag (i.e., 0.917 per ppm) is the preferred estimate for environmental exposure levels. Estimates from the continuous variable Cox regression models are presented for comparison only. As one can see, the continuous variable cumulative exposure model, with its extreme sublinearity in the lower exposure region, yields a substantially lower unit risk estimate (0.0146 per ppm), while the log cumulative exposure model, with its extreme supralinearity in the lower exposure region, yields a substantially higher unit risk estimate (80.6 per ppm). Converting the units, 0.917 per ppm corresponds to a unit risk of 5.01×10^{-4} per $\mu g/m^3$ for lymphohematopoietic cancer mortality in males.

As discussed in Section 4.1.1.1, risk estimates based on Steenland et al.'s (2004) "lymphoid" cancer results are also derived, for comparison. The same methodology presented above for the lymphohematopoietic cancer results was used for the "lymphoid" cancer risk estimates. Age-specific background mortality rates for the relevant subcategories (NHL [C82-C85 of 10^{th} revision of ICD], multiple myeloma [C88,C90], and lymphoid leukemia [C91]) of lymphohematopoietic cancer in males for the year 2001 were obtained from the NCHS Data Warehouse website (http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs.htm). The Steenland et al. Cox regression results for the cumulative exposure models for "lymphoid" cancer in males are presented in Table 8. As for lymphohematopoietic cancer, the best-fitting model was for log cumulative exposure with a 15-year lag (p=0.02), and the cumulative exposure model did not appear to fit the data well for the lower exposure groups (Figure 5). Thus, a linear regression of the categorical results was again performed, dropping the highest exposure group, as described above. The exposure categories, and corresponding average exposures, are the same as for lymphohematopoietic cancer. The linear regression yielded a regression coefficient of 0.000279 per ppm × day (SE = 0.000269 per ppm × day).

The EC_{01}, LEC_{01}, and inhalation unit risk estimates for the different "lymphoid" cancer mortality models examined are presented in Table 9. The results are similar to those based on lymphohematopoietic cancer mortality (i.e., within 35%; see Table 7), especially for the two continuous variable models.

4.1.1.3. *Prediction of Lifetime Extra Risk of Lymphohematopoietic Cancer Incidence*

EPA cancer risk estimates are typically derived to represent an upper bound on increased risk of cancer *incidence*, as from experimental animal incidence data. Cancer data from epidemiologic studies are more generally mortality data, as is the case in the Steenland et al. (2004) study. For tumor sites with low survival rates, mortality-based estimates are reasonable approximations of cancer incidence risk; however, for many lymphohematopoietic cancers, the survival rate is substantial, and incidence-based risks are preferred because EPA endeavors to protect against cancer occurrence, not just mortality (U.S. EPA, 2005a).

Therefore, another calculation was done using the same regression coefficients presented above (Section 4.1.1.2), but with age-specific male lymphohematopoietic cancer incidence rates for 1996–2000 from SEER (NCI, 2003; Tables IX, XVIII, XVII, and XIII: all races) in place of the lymphohematopoietic cancer mortality rates in the actuarial program. SEER collects good-quality cancer incidence data from a variety of geographical areas in the United States. The incidence data used here are from "SEER 9," a registry of nine states and cities covering about 10% of the U.S. population.

The incidence-based calculation assumes that lymphohematopoietic cancer incidence and mortality have the same exposure-response relationship for the relative rate of effect from EtO exposure and that the incidence data are for first occurrences of primary lymphohematopoietic cancer or that relapses and secondary lymphohematopoietic cancers provide a negligible contribution. (The latter assumption is probably sound; the former assumption is more potentially problematic. Because various lymphohematopoietic subtypes with different survival rates are included in the categorization of all lymphohematopoietic cancers, if the relative rates of the subtypes differ and if the relative rate-weighted survival rates for all lymphohematopoietic cancers are different from those for the combined subtypes, a bias could occur, resulting in either an underestimation or overestimation of the extra risk for lymphohematopoietic cancer incidence.) The incidence-based calculation also relies on the fact that the lymphohematopoietic cancer incidence rates are small when compared with the all-cause mortality rates. The resulting EC_{01}, LEC_{01}, and inhalation unit risk estimates for lymphohematopoietic cancer incidence in males from the various models examined are presented in Table 7.

The unit risk estimates for cancer incidence range from about 65% (cumulative exposure model) to 120% (log cumulative exposure model) higher than the corresponding mortality-based estimates. The incidence estimate from the categorical results is about 80% higher than the mortality-based estimate.

The preferred estimate for the unit risk for lymphohematopoietic cancer in males is the estimate of 1.64 per ppm (8.99×10^{-4} per $\mu g/m^3$) derived, using incidence rates for the cause-

specific background rates, from the categorical results of Steenland et al.'s (2004) internal exposure-response modeling.

As discussed in Section 4.1.1.1, risk estimates based on Steenland et al.'s (2004) "lymphoid" cancer results are also derived, for comparison. The same methodology presented above for the lymphohematopoietic cancer results was used for the "lymphoid" cancer incidence risk estimates. Age-specific SEER incidence rates for the relevant subcategories (NHL, myeloma, and lymphocytic leukemia) of lymphohematopoietic cancer in males for the years 1997-2001 were used (NCI, 2004a). The EC_{01}, LEC_{01}, and inhalation unit risk estimates for "lymphoid" cancer incidence from the different "lymphoid" cancer mortality models examined are presented in Table 9. The results are similar to those for lymphohematopoietic cancer incidence (i.e., within 30%; see Table 7), especially for the two continuous variable models.

4.1.2. Risk Estimates for Breast Cancer

4.1.2.1. *Breast Cancer Results From the NIOSH Study*

The Steenland et al. (2004) study discussed above in Section 4.1.1.1 also presents results from exposure-response analyses for breast cancer mortality in female workers. Steenland et al. (2003) present results of a breast cancer incidence study of a subcohort of the female workers from the NIOSH cohort.

4.1.2.2. *Prediction of Lifetime Extra Risk of Breast Cancer Mortality*

The Cox regression modeling results presented by Steenland et al. (2004) and summarized in Table 10 were used for predicting the extra risks for breast cancer mortality in females from continuous environmental exposure to EtO, applying the methodologies described in Section 4.1.1.

U.S. age-specific all-cause mortality rates for 1999 for females of all race groups combined (NCHS, 2002) were used to specify the all-cause background mortality rates in the actuarial program. The National Center for Health Statistics 1997–2001 cause-specific background mortality rates for invasive breast cancers in females were obtained from a Surveillance, Epidemiology, and End Results (SEER) report (NCI, 2004a). The risks were computed up to age 85 for continuous exposures to EtO, conversions were made between occupational EtO exposures and continuous environmental exposures, and 95% UCLs were calculated for the relative rates, as described above.

The best-fitting Cox regression model presented by Steenland et al. (2004) for breast cancer mortality in females was for log cumulative exposure with a 20-year lag (p=0.01). However, as for the lymphohematopoietic cancers in Section 4.1.1, using the log cumulative exposure model to estimate the risks from low environmental exposures is problematic because

this model is highly supralinear and results are unstable for low exposures (see Figure 6). The (continuous variable) cumulative exposure model, which is typically used and which is stable at low exposures, did not provide a good fit to the breast cancer mortality data (p=0.34). In addition, the continuous variable Cox regression model with cumulative exposure is sublinear for low exposures and would not reflect the apparent supralinearity of the data.

It was again determined that the best way to reflect the data in the lower exposure region, which is the region of interest for low-exposure extrapolation, was to do a weighted linear regression of the results from the model with categorical cumulative exposure (and a 20-year lag), excluding the highest exposure group. The weights used for the ORs were the inverses of the variances, which were calculated from the confidence intervals. Mean and median exposures for the cumulative exposure groups were kindly provided by Dr. Steenland (e-mail dated May 26, 2004, from Kyle Steenland, Emory University, to Jennifer Jinot, U.S. EPA).[4] The mean values were used for the weighted regression analysis because the cancer response is presumed to be a function of cumulative exposure, which is expected to be best represented by mean exposures. If the median values had been used, a slightly larger regression coefficient would have been obtained, resulting in slightly larger risk estimates.

Using this approach, a regression coefficient of 0.000201 per ppm × day (SE = 0.000120 per ppm × day) was obtained from the weighted linear regression of the categorical results. These parameter estimates were used for the primary risk calculations for breast cancer mortality in females. Risk calculations using the Cox model results for the continuous log cumulative exposure variable (Table 10) were also performed for comparison. No risk estimates were derived based on the continuous cumulative exposure model results because of the poor fit for this model (p=0.34).

Point estimates and one-sided 95% UCLs for the extra risk of breast cancer mortality in females associated with varying levels of continuous environmental exposure to EtO based on the Steenland et al. (2004) model results were calculated using the actuarial program; the results are presented in Table 11 (point estimates only are presented from the continuous log cumulative exposure variable comparison model). The model based on (categorical) cumulative exposure yields extra risk estimates that are fairly linear for exposures below 0.1 ppm. The risk estimates based on log cumulative exposure, on the other hand, are not (low-dose) linear even in the range of 0.0001 to 0.001 ppm, the lowest exposure concentrations evaluated (i.e., not linear through zero exposure).

[4]Mean exposures for females with a 20-year lag for the categorical exposure quartiles in Table 10 were 276; 1,453; 5,869; and 26,391 ppm × days. Median values were 250; 1,340; 5,300; and 26,676 ppm × days. These values are for the risk sets but should provide a good approximation to the full cohort values.

The same data and methodology were also used to estimate the exposure level (EC_x; "effective concentration") and the associated 95% lower confidence limit (LEC_x) corresponding to an extra risk of 1% (x = 0.01). As discussed in Section 4.1.1, a 1% extra risk level is a more reasonable response level for defining the POD for these epidemiologic data than 10%. Based on the actuarial program, the risk ratio for an extra risk of 1% for breast cancer mortality is 1.4, which better corresponds with the ORs reported by Steenland et al. (2004) than the higher risk ratio of 4.9 that would be associated with a 10% extra risk. In fact, for the linear model that was selected, the unit risk is independent of the benchmark risk level used to determine the POD; however, selection of a benchmark risk level is useful for comparisons across models.

Because EtO is clearly mutagenic, a linear low-dose extrapolation was performed, in accordance with EPA's *Guidelines for Carcinogen Risk Assessment*. The EC_{01}, LEC_{01}, and inhalation unit risk estimates for the different breast cancer mortality models examined are presented in Table 12. As discussed above, the unit risk estimate based on linear regression of the Steenland et al. (2004) categorical results using cumulative exposure with a 20-year lag (i.e., 0.513 per ppm) is the preferred estimate for breast cancer mortality risks from environmental exposures. Estimates from the continuous log cumulative exposure variable model are presented for comparison only. The log cumulative exposure model, which is supralinear in the lower exposure region, yields a substantially higher unit risk estimate (45.7 per ppm). In this case, the supralinear model appears to better approximate the lower exposure categorical data than for lymphohematopoietic cancer (See Figures 4 and 6), but it is difficult to obtain stable unit risk estimates from this model. Furthermore, there is uncertainty around the RR estimates; thus, in the absence of mechanistic data to support a supralinear model, it seems appropriate to use the results of the linear (regression) model, as EPA typically does for categorical epidemiologic data. Converting the units, 0.513 per ppm corresponds to a unit risk of 2.80×10^{-4} per $\mu g/m^3$.

4.1.2.3. *Prediction of Lifetime Extra Risk of Breast Cancer Incidence*

As discussed in Section 4.1.1.3, risk estimates for cancer incidence are preferred to estimates for cancer mortality. In the case of female breast cancer in the NIOSH cohort, there is a corresponding incidence study (Steenland et al., 2003) with exposure-response results for breast cancer incidence, so we can estimate cancer incidence risks directly rather than estimate them from mortality data. The incidence study used a subcohort of 7,576 (76%) of the female workers from the original cohort. Subcohort eligibility was restricted to the female workers who had been employed at 1 of the 14 plants for at least 1 year, owing to cost considerations and the greater difficulties in locating workers with short-term employment. Completed questionnaires were received for 5,139 (68%) of the 7,576 women in the subcohort. The investigators also attempted to acquire breast cancer incidence data for the entire subcohort from cancer registries (available

for 9 of the 11 states in which the plants were located) and death certificates; thus, results are presented for both the full (sub)cohort (n = 7,576) and the subcohort of women with completed questionnaires (n = 5,139). For additional details and discussion of the Steenland et al. (2003) study, see Appendix A.

Steenland et al. (2003) identified 319 incident cases of breast cancer in the cohort through 1998. Interview (questionnaire) data were available for 73% (233 cases). Six percent were carcinoma in situ (20 cases). Steenland et al. (2003) performed internal exposure-response analyses similar to those described in their 2004 paper and in Section 4.2.1 above. Controls for each case were selected from the cohort members without breast cancer at the age of diagnosis of the case. Cases and controls were matched on race. Of the potential confounders evaluated for those with interviews, only parity and breast cancer in a first-degree relative were important predictors of breast cancer, and only these variables were included in the final models for the subcohort analyses. In situ cases were included with invasive breast cancer cases in the analyses; however, the in situ cases represent just 6% of the total, and excluding them reportedly did not greatly affect the results.

For internal analyses using the full cohort, the best-fitting model with exposure as a continuous variable was for (natural) log cumulative exposure, lagged 15 years (p=0.05). Duration of exposure, lagged 15 years, provided a slightly better fitting model. Models using maximum or average exposure did not fit as well. In addition, use of a threshold model did not provide a statistically significant improvement in fit. For internal analyses using the subcohort with interviews, the cumulative exposure and log cumulative exposure models, both lagged 15 years, and the log cumulative exposure model with no lag all fit almost equally well, and the duration of exposure (also lagged 15 years) model fit slightly better. Results of the Cox regression analyses for the cumulative and log cumulative exposure models, with 15-year lags, are shown in Table 13, and these are the results used for the unit risk calculations. The models using duration of exposure are less useful for estimating exposure-related risks, duration of exposure and cumulative exposure are correlated, and the fits for these models are only marginally better than those with cumulative exposure. The log cumulative exposure model with no lag was considered less biologically realistic than the corresponding model with a 15-year lag because some lag period would be expected for the development of breast cancer. Furthermore, although risk estimates based on the full cohort results are calculated for comparison, the preferred estimates are those based on the subcohort with interviews because the subcohort should have complete case ascertainment and has additional information available on potential breast cancer confounders.

For the actuarial program, U.S. age-specific all-cause mortality rates for 1999 for females of all race groups combined (NCHS, 2002) were used to specify the all-cause background

mortality rates. Because breast cancer incidence rates are not negligible compared to all-cause mortality rates, the all-cause mortality rates in the life-table analysis were adjusted to reflect women dying *or* acquiring incident cases of breast cancer in a given age interval. All-cause mortality rates and breast cancer incidence rates were summed, and breast cancer mortality rates were subtracted so that those dying of breast cancer were not counted twice (i.e., as deaths and as incident cases of breast cancer). The National Center for Health Statistics 1997–2001 mortality rates for invasive breast cancer in females were obtained from a SEER report (NCI, 2004a). The SEER report also provided SEER–9 incidence rates for invasive and in situ breast cancer. The Cox regression results reported by Steenland et al. (2003) are for invasive and in situ breast cancers combined. It is consistent with EPA policy to combine these two tumor types because the in situ tumors can progress to invasive tumors. Thus, the primary risk calculations in this assessment use the sum of invasive and in situ breast cancer incidence rates for the cause-specific background rates. Comparison calculations are performed using just the invasive breast cancer incidence rates for the cause-specific rates; this issue is further discussed in Section 4.1.3 on sources of uncertainty. The risks were computed up to age 85 for continuous exposures to EtO, conversions were made between occupational EtO exposures and continuous environmental exposures, and 95% UCLs were calculated for the relative rates, as described above.

For breast cancer incidence in both the full cohort (Figure 7) and the subcohort with interviews (Figure 8), the categorical data suggest a more linear exposure-response relationship than that obtained with either the continuous variable log cumulative exposure (supralinear) or cumulative exposure (sublinear) models. Thus, as with the lymphohematopoietic cancer and the breast cancer mortality results above, it was determined that the best way to reflect the data in the lower exposure region, which is the region of interest for low-exposure extrapolation, was to do a weighted linear regression of the results from the model with categorical cumulative exposure (with a 15-year lag). In addition, the highest exposure group was not included in the regression to provide a better fit to the lower exposure data. The weights used for the ORs were the inverses of the variances, which were calculated from the confidence intervals. Mean and median exposures for the cumulative exposure groups for the full cohort were kindly provided by Dr. Steenland (e-mail dated April 21, 2004, from Kyle Steenland, Emory University, to Jennifer Jinot, U.S. EPA).[5] The mean values were used for the weighted regression analysis because the (arithmetic) mean exposures best represent the model's linear relationship between exposure and cancer response. Differences between means and medians were not large for the females, especially for the lower

[5]Mean exposures for females with a 15-year lag for the exposure categories in Table 3 were 280; 1,241; 3,304; 8,423; and 36,022 ppm × days. Median values were 253; 1,193; 3,241; 7,741; and 26,597 ppm × days. These values are for the risk sets but should provide a good approximation to the full cohort values.

four quintiles. If the median values had been used, a slightly larger regression coefficient would have been obtained, resulting in slightly larger risk estimates. Although the exposure values are for risk sets from the full cohort, they should be reasonably close to the values for the subcohort with interviews.

Using this approach, a regression coefficient of 0.0000264 per ppm × day (SE = 0.0000269 per ppm × day) was obtained from the weighted linear regression for the full cohort, and a regression coefficient of 0.0000517 per ppm × day (SE = 0.0000369 per ppm × day) was obtained for the subcohort of women with interviews. The regression coefficients and standard errors from the weighted linear regression of the categorical results were used for the primary risk calculations for breast cancer incidence. Risk estimates based on the model results for the continuous exposure variables (i.e., cumulative exposure and log cumulative exposure; see Table 13) are also derived for comparison.

The resulting EC_{01}, LEC_{01}, and inhalation unit risk estimates for breast cancer incidence in females from the various models examined are presented in Tables 14 (invasive and in situ) and 15 (invasive only). The primary calculation for invasive and in situ breast cancer incidence based on the linear regression coefficient from the categorical results (without the highest exposure group) in the subcohort of women with interviews yielded an EC_{01} of 0.024 ppm, an LEC_{01} of 0.011 ppm, and a unit risk estimate of 0.909 per ppm. The comparable unit risk estimate for the full cohort is about 40% lower. One would expect this value to be lower because of incomplete case ascertainment in the full cohort. The corresponding unit risk estimate derived based on the subcohort results but using invasive breast cancer only for the background incidence rates is about 17% lower, reflecting the difference between incidence rates for invasive breast cancer only and for combined in situ and invasive breast cancer. The unit risk estimate of 0.909 per ppm is the preferred estimate for female breast cancer risk because it is based on incidence data versus mortality data, it is based on more cases (n = 233) than the mortality estimate (n = 103), and information on personal breast cancer risk factors obtained from the interviews is taken into account. Converting the units, 0.909 per ppm corresponds to a unit risk of 4.97×10^{-4} per $\mu g/m^3$.

4.1.3. Sources of Uncertainty in the Cancer Risk Estimates

The two major sources of uncertainty in quantitative cancer risk estimates are generally from interspecies extrapolation and high-dose to low-dose extrapolation. The risk estimates derived from the Steenland et al. (2003, 2004) analyses are not subject to interspecies uncertainty because they are based on human data. Furthermore, the human-based estimates suffer less from high-dose to low-dose extrapolation than do rodent-based estimates and, thus, uncertainty from that source is reduced somewhat. For example, the average exposure in the NIOSH cohort was more than 10 times lower than the lowest exposure level in a rodent bioassay after adjustment to

continuous lifetime exposure. Nonetheless, some 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 clear evidence of EtO mutagenicity supports the linear low-dose 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), 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 areas of inevitable uncertainties 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. Detailed work history data for the individual workers were collected for the 1987 followup (Steenland et al., 1991). For the extended followup (Steenland et al., 2003, 2004), additional information on the date last employed was obtained for those workers still employed and exposed at the time of the original work history collection for the plants still using EtO (25% of the cohort). It was then assumed that exposure for these workers continued until the date of last employment and that their exposure level stayed the same as that in their last job held at the time of the original data collection. Thus, there would be more exposure misclassification in the extended followup. However, when the investigators compared cumulative exposures estimated with and without the extended work histories, they found little difference because exposure levels were very low by the mid-1980s and, therefore, had little impact on cumulative exposure (Steenland et al., 2003, 2004). While the NIOSH regression model performed very well in estimating exposures in validation tests (Hornung et al., 1994), there is, nonetheless, considerable uncertainty associated with any retrospective exposure assessment, and this can affect the ability to discriminate among exposure-response models.

With respect to the male lymphohematopoietic cancer response (Steenland et al., 2004), it must be noted that all attempts at exposure-response modeling are limited by the small number of cases (n = 37). 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. Normally, model dependence should be minimized by the practice, under EPA's 2005 *Guidelines for Carcinogen Risk Assessment*, of modeling only in the observable range and then performing a linear extrapolation from the "POD" (in this case the LEC_{01}).

However, the log cumulative exposure Cox regression model with 15-year lag, which provides the best fit to the overall data, is too steep in the low-exposure region and then plateaus rapidly, making it difficult to derive stable risk estimates (i.e., estimates that are not highly dependent on the POD). And the alternative (continuous variable) cumulative exposure model, though typically used for epidemiologic data, is too sublinear in the low-exposure region for these data, which exhibit supralinearity. Thus, a weighted linear regression of the categorical cumulative exposure (with 15-year lag) results (dropping the highest exposure group) was used in this assessment to better represent the data in the lower exposure region. Dropping the highest two exposure groups was not done because it is desirable to use as much of the data as reasonably possible and because the second-highest exposure group is not so far from potential environmental exposure levels (unlike the highest exposure group, which reflects much higher exposures). It should also be noted that the various models gave similar risk estimates for the subcategory of "lymphoid" cancer in males as were obtained for all lymphohematopoietic cancer.

Although linear regression of the categorical results seems to be a reasonable approach for best reflecting the exposure-response results at the lower end of the exposure range, clearly there is uncertainty regarding the exposure-response model, as suggested by the range of risk estimates resulting from the different models (Table 7). The best-fitting continuous exposure model (the log cumulative exposure model) yields a higher unit risk estimate, but the unit risk based on the linear regression of the categorical results is preferred because it is more stable. Linear modeling of categorical epidemiological results is a standard technique used by EPA (U.S. EPA, 2005a).

Another area of uncertainty related to the exposure-response modeling is the lag period. The best-fitting models presented by Steenland et al. (2004) for lymphohematopoietic cancer had a 15-year lag (lag periods of 0, 5, 10, 15, and 20 years were explored). Lymphohematopoietic cancers are thought to generally (but not always) have a relatively short latency period, but a 15-year lag period means that exposures in the 15 years prior to death or the end of followup are not taken into account. In other words, in the best-fitting models, relevant exposures for the development of the lymphohematopoietic cancers occurred over 15 years before death. Yet, the analyses of the investigators indicate that the regression coefficient for cumulative exposure might have decreased with followup, suggesting that the higher exposure levels encountered by the workers in the more distant past are having less of an impact on current risk. The regression coefficient was 1.12×10^{-5} per ppm × day, for both sexes with a 10-year lag, in the 1987 followup (Stayner et al., 1993) versus 4×10^{-6} per ppm × day, for males with no lag, in the 1998 followup (Steenland et al., 2004). The earlier value was for males and females, but even then the lymphohematopoietic cancer response was observed predominantly in males, so a regression coefficient for males only would have been even greater. On the other hand, with no lag period,

as for the more recent coefficient for cumulative exposure, the earlier value would have been diminished somewhat.

The life-table analysis used in this risk assessment accrues exposure over the full lifetime for the cumulative exposure metric. If, in fact, exposures in the distant past cease to have a meaningful impact on risk of lymphohematopoietic cancer, this approach would tend to overestimate the unit risk. Thus, a comparison analysis was conducted to evaluate the impact of ignoring exposures over 55 years in the past in the life-table analysis. The actual value of such a cut-point, if warranted, is unknown. A value less than 55 years might not be appropriate because exposures for some of the workers began in 1943, so any diminution of potency for past exposures occurring since 1943 is already reflected in the regression coefficient with followup through 1998, at least for those workers, although it is unknown what proportion of workers had such early exposures and how long they survived. The comparison analysis yielded an LEC_{01} of 0.00815 ppm and a unit risk estimate of 1.23 per ppm, which is 25% less than the estimate obtained from the unrestricted life-table analysis. Because the appropriate cut-point for excluding past exposures is unknown and the unit risk estimate from the linear regression is already substantially less than that obtained from the best-fitting model, the estimate from the full life-table analysis is preferred.

Several dose metrics (cumulative exposure, duration of exposure, maximum [8-hour TWA] exposure, and average exposure) were analyzed by the investigators, and cumulative exposure was the best predictor of mortality from lymphohematopoietic 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 their analysis, and the plants included in this cohort were specifically selected for the absence of any known confounding exposures (Stayner et al., 1993). The linear regression discussed above is based on the categorical data for the males only. A concern about the results of this study is the observation of increased risks of lymphohematopoietic cancers in males but not in females. In females, increased ORs were observed in the second exposure quartile for lymphohematopoietic cancer and in the second and third quartiles for "lymphoid" cancer compared to the lowest quartile, but there is no evidence of a positive exposure-response relationship overall. Average exposures in males (mean 37.8 ppm, standard deviation 87.6 ppm, median 7.6 ppm) were higher than in females (mean 18.2 ppm, standard deviation 38.2 ppm, median 4.6 ppm), but, according to Steenland et al. (2004), there was enough variation in the exposures in females to have observed an exposure-response relationship if one existed. There is no known biological basis for this observed discrepancy in the lymphohematopoietic cancer response between males and females, and no such sex-specific effect is suggested by the rodent data. In the NTP (1987) mouse bioassay, only females had EtO-

induced lymphohematopoietic cancer (malignant lymphoma), whereas in the Snellings et al. (1984) rat study both males and females had EtO-induced lymphohematopoietic cancer (mononuclear cell leukemia), and the risk in females was slightly higher than that in males (Table 3).

As for the other epidemiological studies that included females, they generally had too few lymphohematopoietic cancer cases to reveal much about the possible risks to females. In the Hogstedt et al. (1988) study, there were 3 leukemias in 170 women versus 0.2 expected. In the Hagmar et al. (1991, 1995) study of 1309 women and 861 men, there was an SIR of 1.78 for lymphohematopoietic cancer and an SIR of 2.44 for leukemia, but there was no breakdown by sex. In the Norman et al. (1995) study, one leukemia case was observed in 928 women versus 0.41 expected. In the Kardos et al. (2003) study of 233 females, there were 11 cancer deaths versus 4.03–4.38 expected; one of these deaths was from lymphoid leukemia, but expected deaths by cancer type were not provided. In the Coggon et al. (2004) study of 1012 women and 1864 men, there were 17 lymphohematopoietic cancer deaths versus 12.9 expected. No breakdown by sex was provided; however, 12 of these 17 deaths were in chemical workers (vs. 7.9 expected, i.e., all of the observed excess was in the chemical workers, as opposed to the hospital workers), and all but one of the chemical workers were male. Coggon et al. claim that it seems unlikely that either peak or average exposures to EtO were markedly higher in the chemical workers than in the hospital workers, but they acknowledge that this claim is based on limited exposure data. Thus, the Coggon et al. results are consistent with a higher risk of lymphohematopoietic cancer in males than in females; however, the data are insufficient to infer anything.

With respect to the breast cancer mortality response (Steenland et al., 2004), the exposure-response modeling was based on 103 deaths. As for the lymphohematopoietic cancer response in males, the exposure-response data for breast cancer mortality are fairly supralinear, especially for the low-exposure groups. Thus, the same approach of using a weighted linear regression of the categorical results with the highest exposure group excluded was taken to obtain a regression coefficient for the life-table analysis. As shown in Table 12, the unit risk estimate obtained from this approach is substantially lower than that obtained from the log cumulative exposure model. Nonetheless, the linear regression approach is considered appropriate because the log cumulative exposure model generates unstable risk estimates, there is uncertainty in the RR models, and a linear exposure-response model is the default model typically used by EPA for categorical human cancer data (U.S. EPA, 2005a). For the lag period, the best-fitting model had a lag of 20 years, which was longest lag period investigated. This is a commonly used lag period for solid tumors, which typically have longer latency periods than lymphohematopoietic cancers. It is unknown whether a lag period longer than 20 years would have provided a better model fit. The Steenland et al. (2004) analysis took into account age, race, and calendar time. Other risk factors for breast

cancer could not be included in the mortality analysis, but many of these factors were considered in the breast cancer incidence study (Steenland et al., 2003), as discussed below.

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 lymphohematopoietic cancer. Further advantages to using the results from the incidence study are that more cases were available for the Cox regression modeling (319 cases) and that the investigators were able to include data on potential confounders in the modeling for the subcohort with interviews (233 cases). For the full cohort, the cumulative exposure model providing the best fit to the data was again the log cumulative exposure model. With breast cancer incidence, a 15-year lag provided the best model fits. For the subcohort, the cumulative exposure and log cumulative exposure models fit nearly equally well. For both groups, the categorical data 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 (Figures 6 and 7). Thus, for both groups, a linear regression was fit through the categorical results, dropping the highest exposure group to provide a better fit to the lower exposure data.

As can be seen in Tables 14 and 15, there is substantial variation in the risk estimates obtained from these different models. The categorical data for breast cancer incidence do not display the supralinearity in the lower exposure groups seen in the cases discussed above (with the inclusion of the highest exposure group, some supralinearity is evident); thus, the difference between the unit risk estimates from the cumulative exposure model and the linear regression model are not as dramatic as seen in those cases (the linear regression results are less than sevenfold higher).

An area of uncertainty in the life-table analysis for breast cancer incidence pertains to the rates used for the cause-specific background rate. The regression coefficients presented by Steenland et al. (2003) represent invasive and in situ cases combined, where 6% of the cases are in situ, and the preferred unit risk estimates in this assessment are calculated similarly using background rates for invasive and in situ cases combined. The regression coefficients for invasive and in situ cases combined should be good approximations for a regression coefficients for invasive cases alone; however, it is uncertain how well they reflect the exposure-response relationships for in situ cases alone. Diagnosed cases of in situ breast cancer would presumably be remedied and not progress to invasive breast cancer, so double-counting is unlikely to be a significant problem. Carcinoma in situ is a risk factor for invasive breast cancer; however, this observation is most likely explained by the fact that these two types of breast cancer have other breast cancer risk factors in common, some of which have been considered in the subcohort analysis. One might hypothesize that EtO exposure could cause a more rapid progression to

invasive tumors; however, there is no specific evidence that this occurs. On the other hand, there is some indication that in situ cases in the incidence study might have been diagnosed at relatively low rates in comparison to the invasive cases. Steenland et al. (2003) reported that 6% of the cases in their study are in situ; according to the National Cancer Institute; however, ductal carcinoma in situ accounted for about 18% of newly diagnosed cases of breast cancer in 1998 (NCI, 2004b).

There are several possible explanations for this difference. One is that it reflects differences in diagnosis with calendar time because the rate of diagnosis of carcinoma in situ has increased over time with increased use of mammography. Another is that the difference is partially a reflection of the age distribution in the cohort because the proportion of new cases diagnosed as carcinoma in situ varies by age. A third possible explanation is that the low proportion of in situ cases is at least partially a consequence of underascertainment of cases because in situ cases will not be reported on death certificates, although, even if all 20 in situ cases were in the subcohort with interviews, that would still be only 8.6% of the cases. In any event, this is a relatively minor source of uncertainty, and a comparison of the unit risk estimates in Tables 14 (invasive + in situ) and 15 (invasive only) shows that the preferred estimate of 0.909 per ppm is less than 20% higher than the corresponding estimate using only invasive breast cancer background rates.

The results for the subcohort with interviews are used for the primary breast cancer unit risk calculations because, in addition to including the data on potential confounders, the subcohort is considered to have full ascertainment of the breast cancer cases, whereas the full cohort for the incidence study has incomplete case ascertainment, as illustrated by the fact that death certificates were the only source of case ascertainment for 14% of the cases. Thus, risk estimates based on the full cohort would be underestimated; nevertheless, these estimates were calculated for comparison with the subcohort estimates. As can be seen in Table 14, the preferred unit risk estimate of 0.909 per ppm is about 60% higher than the corresponding estimate from the full cohort.

With respect to dose metrics for breast cancer incidence, models using duration provided better model fits than those using cumulative exposure; however, duration is less useful for estimating unit risks and the cumulative exposure models also provided a statistically significant fit 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, analyses for the full cohort were adjusted for age, race, and calendar time, and exposures to other chemicals in these plants were reportedly minimal. For the subcohort with interviews, a number of specific breast cancer risk factors were investigated, 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.

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. From experimental animal studies, this is accomplished by using tumor incidence data and summing across all the tumor sites that demonstrate significantly increased incidences, customarily for the most sensitive sex and species, to be protective of the general human population. However, in estimating comparable risks 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 lymphohematopoietic cancer (for breast cancer, a separate incidence study [Steenland et al., 2003] was performed). Second, these occupational epidemiology data represent a healthy-worker cohort. Third, the epidemiologic study may not have sufficient statistical power and followup 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 lymphohematopoietic cancer risk estimates. Although assumptions are made in using incidence rates for the cause-specific background rates, as discussed in 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. 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”.

With respect to other possible tumor sites of concern, the rodent data suggest that lymphohematopoietic cancers are the major (or a close second) tumor type associated with EtO exposure in female mice and in male and female rats. Thus, it is reasonable to expect 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 followup (mean length of followup 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.

Despite these uncertainties, the inhalation cancer unit risk estimates of 1.64 per ppm for male lymphohematopoietic cancer incidence and 0.909 per ppm for female breast cancer incidence have the advantages of being based on human data from a high-quality epidemiologic study with individual exposure estimates for each worker. In addition, the similarity of the estimates for these two different tumor responses, one in males and one in females, provides support for the use of these estimates to represent the risk in humans. The male lymphohematopoietic cancer incidence risk estimate was also similar to the estimate of 1.20 per ppm based on the subcategory of "lymphoid" cancers in males.

4.1.4. Conclusions

An EC_{01} of 0.024 ppm was calculated using a life-table analysis and linear modeling of the categorical Cox regression analysis results for excess lymphohematopoietic cancer mortality in males reported in a high-quality occupational epidemiology study. Linear low-dose extrapolation from the LEC_{01} yielded a lifetime extra cancer mortality unit risk estimate of 0.92 per ppm of continuous EtO exposure. Applying the same linear regression coefficient and life-table analysis to background lymphohematopoietic cancer *incidence* rates yielded an EC_{01} of 0.013 ppm and a preferred lifetime extra cancer unit risk estimate of 1.64 per ppm (9.0×10^{-4} per $\mu g/m^3$). Use of this unit risk estimate is also expected to be protective of females, based on the lifetime extra cancer unit risk estimate of 0.909 per ppm (5.0×10^{-4} per $\mu g/m^3$; EC_{01} = 0.024 ppm) calculated using the same approach from the results of a breast cancer incidence study of the same worker cohort. (An increased risk of EtO-associated lymphohematopoietic cancer in females cannot be ruled out; however, the Steenland et al. [2004] results suggest that any increased risk to females is likely to be lower than the risk estimated for males, and it is not expected that the combined increased risk to breast cancer and lymphohematopoietic cancer in females would exceed the unit risk estimated for lymphohematopoietic cancer in males.)

4.2. INHALATION UNIT RISK DERIVED FROM EXPERIMENTAL ANIMAL DATA

4.2.1. Overall Approach

Lifetime animal cancer bioassays of inhaled EtO have been carried out in three laboratories, as described in Section 3.2. The data from these reports are presented in Tables 1 through 3. These studies have also been reviewed by the IARC (1994) and Health Canada (2001). Health Canada calculated the ED_{05} for each data set using the benchmark dose methodology. The EOIC report (EOIC, 2001) tabulated only lymphatic tumors because they constituted the predominant risk.

The overall approach in this derivation is to find a unit risk for each of the bioassays—keeping data on males and females separate—from data on the incidence of all tumor types and then to use the maximum of these values as the summary measure of the unit risk from animal studies (i.e., the unit risk represents the most sensitive species and sex). The unit risk for the animals in these bioassays is converted to a unit risk in humans by first determining the continuous exposures in humans that are equivalent to the rodent bioassay exposures and then by assuming that the lifetime incidence in humans is equivalent to lifetime incidence in rodents, as is commonly accepted in interspecies risk extrapolations. For cross-species scaling of exposure levels (see Section 4.2.2 below), an assumption of ppm equivalence is used; thus, no interspecies conversion is needed for the exposure concentrations. Bioassay exposure levels are adjusted to equivalent continuous exposures by multiplying by (hours of exposure/24 hours) and by (5/7) for the number of days exposed per week. The unit risk in humans (risk per unit air concentration) is then assumed to be numerically equal to that in rodents (after adjustment to continuous exposures); the calculations from the rodent bioassay data are shown in Tables 1 through 3.

4.2.2. Cross-Species Scaling

In the absence of chemical-specific information, EPA's 1994 inhalation dosimetry methods (U.S. EPA, 1994) provide standard methods and default scaling factors for cross-species scaling. Under EPA's methodology, EtO would be considered a Category 2 gas because it is reactive and water soluble and has clear systemic distribution and effects. Dosimetry equations for Category 2 gases are undergoing EPA re-evaluation and are not being used at this time. For cross-species scaling of extrarespiratory effects, current practice is to treat Category 2 gases as Category 3 gases. For Category 3 gases, ppm equivalence is assumed (i.e., responses across species are equivalent on a ppm exposure basis), unless the air:blood partition coefficient for the experimental species is less than the coefficient for humans (U.S. EPA, 1994, p. 4-61). In the case of EtO, measured air:blood partition coefficients are 78 in the mouse (Fennell and Brown, 2001), 64 in the rat (Krishnan et al., 1992), and 61 in the human (Csanady et al., 2000); thus, ppm equivalence for cross-species scaling to humans can be assumed for extrarespiratory effects observed in mice and rats. The assumption of ppm equivalence is further supported by the PBPK modeling of Fennell and Brown (2001), who reported that simulated blood AUCs for EtO after 6 hours of exposure to concentrations between 1 ppm and 100 ppm were similar for mice, rats, and humans and were linearly related to the exposure concentration (see Section 3.3.1 and Figure 2). This modeling was validated against measured blood EtO concentrations for rodents and humans. In addition, EOIC (2001) and Health Canada (2001) used ppm equivalence in their risk assessments for EtO; Health Canada applied the equivalence to both extrarespiratory and respiratory effects, whereas EOIC modeled only lymphohematopoietic cancers.

For Category 2 gases with respiratory effects, there is no clear guidance on an interim approach. One suggested approach is to do cross-species scaling using both Category 1 and Category 3 gas equations and then decide which is most appropriate. In this document, the preferred approach was to assume ppm equivalence was also valid for the lung tumors in mice because of the clear systemic distribution of EtO (e.g., see Section 3.1). Treating EtO as a Category 1 gas for cross-species scaling of the lung tumors would presume that the lung tumors are arising only from the immediate and direct action of EtO as it comes into first contact with the lung. In fact, some of the EtO dose contributing to lung tumors is likely attributable to recirculation of systemic EtO through the lung.

If one were to treat EtO as a Category 1 gas for the cross-species scaling of the lung tumor response as a bounding exercise, EPA's 1994 inhalation dosimetry methods present equations for estimating the $RGDR_{PU}$, i.e., the regional gas dose ratio for the pulmonary region, which acts as an adjustment factor for estimating human equivalent exposure concentrations from experimental animal exposure concentrations (adjusted for continuous exposure) (U.S. EPA, 1994, pp. 4-49 to 4-51). These equations rely on parameters describing mass transport of the gas (EtO) in the extrathoracic and tracheobronchial regions for both the experimental animal species (mouse) and humans. Without experimental data for these parameters, it seems reasonable to estimate $RGDR_{PU}$ using a simplified equation and the adjusted alveolar ventilation rates of Fennell and Brown (2001). Fennell and Brown adjusted the alveolar ventilation rates to reflect limited pulmonary uptake of EtO, a phenomenon commonly observed for highly water-soluble gases (Johanson and Filser, 1992). The adjusted ventilation rates were then used by Fennell and Brown in their PBPK modeling simulations, and good fits to blood concentration data were reported for both the mouse and human models. In this document, the adjusted alveolar ventilation rates were used to estimate the $RGDR_{PU}$ as follows:

$$RGDR_{PU} = (RGD_{PU})_m/(RGD_{PU})_h = (Q_{alv}/SA_{PU})_m/(Q_{alv}/SA_{PU})h,$$

where:

RGD_{PU} = regional gas dose to the pulmonary region,
Q_{alv} = (adjusted) alveolar ventilation rate,
SA_{PU} = surface area of the pulmonary region, and
the subscripts "m" and "h" denote mouse and human values.

Then, using adjusted alveolar ventilation rates from Fennell and Brown (2001) and surface area values from EPA (U.S. EPA, 1994, p. 4-26),

$$RGDR_{PU} = ((0.78\ L/h)/(0.05\ m^2))/((255\ L/h)/(54.0\ m^2) = 3.3.$$

Using this value for the $RGDR_{PU}$ would increase the human equivalent concentration about threefold, resulting in a decreased risk for lung tumors of about threefold, as a lower bound. The true value of the $RGDR_{PU}$ is expected to be between 1 and 3, and any adjustment to the lung tumor risks would still be expected to result in unit risk estimates roughly within the range of the rodent unit risk estimates derived later in Section 4.2 under the assumption of ppm equivalence.

4.2.3. Dose-Response Modeling Methods

In this document we proceed with the following steps:

1. *Extract the incidence data presented in the original studies.* Our procedure differs in only minor respects from the reviews by IARC (1994) and Health Canada (2001). In the IARC monograph the incidence of brain tumors in the Garman et al. (1985) study was for gliomas alone, whereas we have included all primary brain tumors. In the Health Canada report there was a numerical error in the mid-dose incidence of mononuclear cell leukemia in the Lynch et al. (1982, 1984) study. From the NTP (1987) study Health Canada tabulated only carcinomas of the lung, whereas we included lung adenomas as well as carcinomas. In order to crudely adjust for early mortality in the analysis of the NTP (1987) data, we have corrected the incidence data for a specific tumor type by eliminating the animals that died prior to the occurrence of the first tumor or prior to 52 weeks, whichever was earlier. It was not possible to make this adjustment with the other studies where data on individual animals were not available. With these exceptions, the tumor incidence data in Tables 1 through 3 match the original data, the Health Canada data, and IARC incidence data.

2. *Fit the multistage model to the dose-response data using the Tox_Risk program.* The likelihood-ratio test was used to determine the lowest value of the multistage polynomial degree that provided the best fit to the data while requiring selection of the most parsimonious model. In this procedure, if a good fit to the data in the neighborhood of the POD is not obtained with the multistage model because of a nonmonotonic reduction in risk at the highest dose tested (as sometimes occurs when there is early mortality from other causes), that data point is eliminated and the model is fit again to the remaining data. Such a deletion was found necessary in two cases (mammary tumors in the NTP study and mononuclear cell leukemia in the Lynch study). The goodness-of-fit measures for the dose-response curves and the parameters derived from them are shown in Appendix D.

In the NTP bioassay, where the individual animal data were available, a time-to-tumor analysis was undertaken to account for early mortality. The general model used in this analysis is the multistage Weibull model:

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z],$$

where P(d,t) represents the probability of a tumor by age t (in bioassay weeks) for dose d (i.e., human equivalent exposure), and the parameter ranges are restricted as follows: $z \geq 1$, $t_0 \geq 0$, and $q_i \geq 0$ for I = 0, 1, ..., k. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death. The analyses were conducted using the computer software Tox_Risk version 3.5, which is based on methods developed by Krewski et al. (1983). Parameters are estimated in Tox_Risk using the method of maximum likelihood.

Tumor types can be categorized by tumor context as either fatal or incidental. Incidental tumors are those tumors thought not to have caused the death of an animal, whereas fatal tumors are thought to have resulted in animal death. Tumors at all sites were treated as incidental (although it was recognized that this may not have been the case, the experimental data are not detailed enough to conclude otherwise). The parameter t_0 was set equal to 0 because there were insufficient data to reliably estimate it.

The likelihood-ratio test was used to determine the lowest value of the multistage polynomial degree k that provided the best fit to the data while requiring selection of the most parsimonious model. The one-stage Weibull (i.e., k = 1) was determined to be the most optimal value for all the tumor types analyzed.

3. *Select the POD and calculate the unit risk for each tumor site.* The effective concentration that causes a 10% extra risk for tumor incidence, EC_{10}, and the 95% lower bound of that concentration, LEC_{10}, are derived from the dose-response model. The LEC_{10} is then used as the POD for a linear low-dose extrapolation, and the unit risk is calculated as $0.1/LEC_{10}$. This is the procedure specified in the EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) for agents such as EtO that have direct mutagenic activity. See Section 3.4 for a discussion of the mode of action for EtO. Tables 1 through 3 present the unit risk estimates for the individual tumor sites in each bioassay.

4. *Develop a unit risk estimate based on the incidence of all tumors combined.* This method assumes that occurrences of tumors at multiple sites are independent and, further, that the risk estimate for each tumor type is normally distributed. Then, at a given exposure level, the maximum likelihood estimates (MLEs) of extra risk due to each tumor type are added to obtain the MLE of total cancer risk. The variances corresponding to each tumor type are added to give the variance associated with the sum of the MLEs. The one-sided 95% UCL of the MLE for the combined risk is then calculated as:

$$95\% \text{ UCL} = \text{MLE} + 1.645 \text{s.e.},$$

where s.e. is the standard error and is the square root of the summed variance. (Note that as a precursor to this step, when Tox _Risk is used to fit the incidence of a single tumor type, it provides the MLE and 95% UCL of extra risk at a specific dose. The standard error in the MLE is determined using the above formula). The calculation is repeated for a few exposure levels, and the exposure yielding a value of 0.1 for the upper bound on extra risk is determined by interpolation. The unit risk is then the slope of the linear extrapolation from this POD. The results are given in Table 14.

4.2.4. Description of Experimental Animal Studies

NTP (1987) exposed male and female B6C3F$_1$ mice to concentrations of 0, 50, and 100 ppm for 6 hours per day, 5 days per week, for 102 weeks. An elevated incidence of lung carcinomas was found in males, and elevated lung carcinomas, malignant lymphomas, uterine adenocarcinomas, and mammary carcinomas were found in females. These data are shown in Table 1.

Lynch et al. (1982, 1984) exposed male F344 rats to 0, 50, and 100 ppm for 7 hours per day, 5 days per week, for 2 years. They found excess incidence of tumors at three sites: mononuclear cell leukemia in the spleen, testicular peritoneal mesothelioma, and brain glioma. In this study the survival in the high-dose group (19%) was less than that of controls (49%), which reduced the incidence of leukemias. In the animals in the high-dose group that survived to the termination of the experiment, the incidence of leukemias was statistically significantly higher than for controls ($p<0.01$). The incidence data are shown in Table 2, uncorrected for the high-dose-group mortality. If the individual animal data were available to perform the correction, the incidence would be higher. Therefore, using these data results in an underestimate of risk.

Snellings et al. (1984) exposed male and female F344 rats to 0, 10, 33, and 100 ppm for 6 hours per day, 5 days per week, for 2 years and described their results for all sites except the brain. In two subsequent publications for the same study, Garman et al. (1985, 1986) described the development of brain tumors in a different set of animals. The Snellings et al. publication reported an elevated incidence of splenic mononuclear cell leukemia and peritoneal mesothelioma in males and an elevated incidence of splenic mononuclear cell leukemia in females. The mortality was higher in the 100 ppm groups than the other three groups for both males and females. The incidence in the animals killed after 24 months is shown in Table 3a. The two Garman et al. publications describe brain tumors in males and females (Table 3b). The brain tumor incidence was much lower than that of the other tumors.

4.2.5. Results of Data Analysis of Experimental Animal Studies

The unit risks calculated from the individual site-sex-bioassay data sets are presented in Tables 1 through 3. The highest unit risk of any individual site is 3.23×10^{-5} per $\mu g/m^3$, and it is for mononuclear cell leukemia in the female rats of the Snellings et al. (1984) study.

Table 17 presents the results of the time-to-tumor method applied to the individual animals in the NTP bioassay, compared with the results from the dose group incidence data in Table 1. This comparison was done for each tumor type separately. The time-to-tumor method of analyzing the individual animals results in generally higher unit risk estimates than does the analysis of dose group data, as shown in Table 17. The ratio is not large (less than 2.2) across the tumor types. (In the case of mammary tumors this ratio is actually less than 1. It must be noted that the incidence at the highest dose [where the incidence was substantially less than at the intermediate dose] was deleted from the analysis of grouped data, whereas it was retained in the time-to-tumor analysis. Therefore, the comparison for the mammary tumors is not a strictly valid comparison of methods.) The results also show the extent to which a time-to-tumor analysis of individual animal data increases the risk estimated from data on dose groups. It is expected that if individual animal data were available for the Lynch et al. (1982, 1984) and the Snellings et al. (1984) bioassays, then the time-to-tumor analysis would also result in higher estimates because both those studies also showed early mortality in the highest dose group.

The results of combining tumor types are summarized in Table 16. The sums of the individual unit risks tabulated in Tables 1 to 3 are given in the second row of Table 16. Note that as expected they are greater than the unit risks computed from the upper bound on the sum of risks for all data sets except for the Lynch et al. (1982, 1984) data. The reason for this exception is not known, but the differences are small. It is likely that the problem arises from the methodology used to combine the risks across tumor sites. In an attempt to be consistent with the new two-step methodology (i.e., modeling in the observable range to a POD and then doing a linear extrapolation to 0 extra risk at 0 exposure), the exposure concentration at which the sum of the independent tumor site risks yielded a 95% upper bound on 10% extra risk was estimated and used as the POD. Summing risks in this way results in a POD for the combined tumor risk that is different (lower) than the points of departure for each individual tumor site risk. Thus, the risk estimate for the sum is not strictly comparable to the individual risks that constitute it. These tumor-site-specific risks were based on points of departure individually calculated to correspond with a 10% extra risk. In any event, adding the upper bound risks of individual tumor sites should overestimate the upper bound of the sum, and the latter is the preferred measure of the total cancer risk since it avoids the overestimate. However, for the exceptional Lynch et al. (1982, 1984) data, the sum of upper bounds, 3.66×10^{-5} per $\mu g/m^3$, is already an overestimate of the total risk, and this value is preferred over the anomalously high value of 4.17×10^{-5} per $\mu g/m^3$ corresponding to

the upper bound on the sum of risks. The latter value is considered to be an excessive overestimate and is therefore not carried over into the summary Table 18. For the Snellings et al. (1984) data sets, the upper confidence bound on the sum of risks is used in the summary Table 18. The results of the sum-of-risks calculations on the NTP bioassay time-to-tumor data are included in the third row of Table 16. The estimate for the NTP females is 4.55×10^{-5} per $\mu g/m^3$, which is higher than the other two measures of total tumor risk in that bioassay. This value is preferable to the other measures because it utilizes the individual animal data available for that bioassay.

Summary of results. The summary of unit risks from the five data sets is shown in Table 18. The data set giving the highest risk (4.55×10^{-5} per $\mu g/m^3$) is the NTP (1987) data on combined tumors in females. The other values are within about a factor of 2 of the highest value.

4.3. INHALATION UNIT RISK ESTIMATES—CONCLUSIONS

For both humans and laboratory animals, tumors occur at multiple sites. In humans, there was a combination of tumors having lymphohematopoietic origins in males and breast cancer in females, and in rodents both lymphohematopoietic tumors and tumors of other sites were observed. From human data, an extra cancer unit risk estimate of 9.0×10^{-4} per $\mu g/m^3$ (1.64 per ppm) was calculated for lymphohematopoietic cancer incidence in males, and a unit risk estimate of 5.0×10^{-4} per $\mu g/m^3$ (0.91 per ppm) was calculated for breast cancer incidence in females. [The male lymphohematopoietic cancer incidence risk estimate was notably similar to the estimate of 1.20 per ppm based on the subcategory of "lymphoid" cancers in males.] Unit risk estimates derived from the three chronic rodent bioassays for EtO ranged from 2.2×10^{-5} per $\mu g/m^3$ to 4.6×10^{-5} per $\mu g/m^3$, about an order of magnitude lower than the estimates based on human data.

The Agency takes the position that human data, if adequate data are available, provide a more appropriate basis than do rodent data for estimating human risks (U.S. EPA, 2005a), primarily because uncertainties in extrapolating quantitative risks from rodents to humans are avoided. Although there is a sizeable difference between the rodent-based and the human-based estimates, the similarity between the unit risk estimates based on the female breast cancer and male lymphohematopoietic cancer results increases confidence in the use of the estimate based on the male lymphohematopoietic cancers. Furthermore, the human data are from a large, high-quality study, with EtO exposure estimates for the individual workers and little reported exposure to chemicals other than EtO. Therefore, the extra cancer unit risk estimate of 1.64 per ppm (9.0×10^{-4} per $\mu g/m^3$) calculated for lymphohematopoietic cancer incidence in males is the preferred estimate for this assessment. This unit risk estimate is greater than the estimate of 0.91 per ppm (5.0×10^{-4} per $\mu g/m^3$) calculated from the results of a breast cancer incidence study of the same worker cohort, and is thus recommended as the potency estimate for Agency use. Although there

was no clear exposure-response relationship for lymphohematopoietic cancer in females in the Steenland et al. (2004) study, an increased risk in females cannot be ruled out. Nonetheless, the Steenland et al. results suggest that if such a risk exists for females, it is likely to be lower than the risk estimated for males. Thus, it is expected that the risk estimated based on lymphohematopoietic cancer in males would be protective for females even if females have an increased risk for both breast cancer and lymphohematopoietic cancer.

Because a mutagenic mode of action for EtO carcinogenicity (see Section 3.3.2) is "sufficiently supported in [laboratory] animals" and "relevant to humans", and as there are no chemical-specific data to evaluate the differences between adults and children, increased early-life susceptibility should be assumed and, if there is early-life exposure, the age-dependent adjustment factors (ADAFs) should be applied, as appropriate, in accordance with EPA's Supplemental Guidance (U.S. EPA, 2005b). Consequently, applying the ADAFs to obtain a full lifetime unit risk estimate yields

$$1.64/\text{ppm} \times ((10 \times 2 \text{ years}/70 \text{ years}) + (3 \times 14/70) + (1 \times 54/70))$$
$$= 2.72/\text{ppm} = 1.5 \times 10^{-3}/(\mu\text{g}/\text{m}^3).$$

Using the above full lifetime unit risk estimate of 2.72 per ppm, the lifetime chronic exposure level of EtO corresponding to an increased cancer risk of 10^{-6} can be estimated as follows:

$$(10^{-6})/(2.72/\text{ppm}) = 4 \times 10^{-7} \text{ ppm} = 0.0004 \text{ ppb} = 0.0007 \ \mu\text{g}/\text{m}^3.$$

[Note that for less-than-lifetime exposures scenarios (or for exposures that vary with age), the adult-based estimate of 1.64 per ppm should be used, but, if there is early-life exposure, the ADAFs should be applied in accordance with EPA's Supplemental Guidance. With respect to the breast cancer estimates, evidence suggests that puberty/early adulthood is a particularly susceptible lifestage for breast cancer (U.S. EPA, 2005b; Russo and Russo, 1999); however, EPA has not, at this time, developed alternate ADAFs to reflect such a pattern of increased early-life susceptibility, and there is currently no EPA guidance on an alternate approach for adjusting for early-life susceptibility to potential breast carcinogens.]

If the linear regression model of the categorical cumulative exposure data used to derive the POD is suitable, the inhalation unit risk estimate presented above, which is calculated based on a linear extrapolation from the POD (LEC_{01}), is expected to provide an upper bound on the risk of cancer incidence. However, for certain applications, such as benefit-cost analyses, estimates of "central tendency" for the risk below the POD are desired. Because a linear regression model was used in the observable range of the human data and the POD was within the low-dose linear range

for extra risk as a function of exposure, linear extrapolation below the LEC_{01} is a straight continuation of the 95% UCL on the linear model used above the LEC_{01}. This is illustrated in Tables 6 and 7, where the 95% UCL on extra risk for lymphohematopoietic cancer mortality in males is about 0.92 per ppm for exposures at or below about 0.01 ppm (Table 6), which is equivalent to the mortality unit risk estimate of 0.92 per ppm derived from the LEC_{01} in Table 7 (rounded to two figures). The same holds for the central tendency (weighted least squares) estimate of the mortality extra risk from the model (0.42 per ppm from Table 6 and 0.01 extra risk divided by the EC_{01} of 0.0238 in Table 7 yields 0.42 per ppm, or 2.3×10^{-4} per $\mu g/m^3$).

The same also holds for the incidence estimates (i.e., the same model is used above and below the POD); thus, one can calculate a central tendency estimate of the extra risk of lymphohematopoietic cancer incidence in males for the linear model below the EC_{01} using the results in Table 7 by calculating $0.01/EC_{01}$, or 0.01/(0.013 ppm), which yields 0.77 per ppm (4.2×10^{-4} per $\mu g/m^3$). Similarly, because the same methodology was used for the breast cancer calculations, one can calculate central tendency estimates for the linear model using the EC_{01} results in Tables 12 and 14, yielding a central tendency extra risk estimate of 0.26 per ppm (1.4×10^{-5} per $\mu g/m^3$) for breast cancer mortality and 0.42 per ppm (2.3×10^{-4} per $\mu g/m^3$) for breast cancer incidence (invasive and in situ, based on results from subcohort with interviews). These central tendency estimates are dependent on the suitability of the linear regression models to reflect the lower end of the observable range as well as on the applicability of the linear models below the observable range. The assumption of low-dose linearity is supported by the mutagenicity of EtO (see Section 3.4). [If these central tendency estimates were to be used for cost-benefit analyses or some other purpose, ADAFs should be applied, as appropriate, in accordance with EPA's Supplemental Guidance, as discussed above.]

4.4. COMPARISON WITH OTHER ASSESSMENTS

The unit risk values derived in this document are compared with those of other assessments in Table 19. One assessment is based on human data (EOIC, 2001; Kirman et al., 2004), and four assessments are based on laboratory animal data (California EPA, 1999; Health Canada, 2001; EOIC, 2001/Kirman et al., 2004; and a study by Granath et al., 1999). The comparisons are discussed in the sections below.

4.4.1. Assessments Based on Human Studies

The EOIC (2001) document uses human leukemia data only and pools data from both the Stayner et al. (1993) and the UCC studies (Teta et al., 1993, 1999). Based on the assumption that leukemias are due to chromosome translocations and that translocations require two independent

events (chromosome breaks), the EOIC used a dose-squared model and derived a unit risk value of 1.8×10^{-7} $(\mu g/m^3)^{-1}$ as the most appropriate value, with a range of 1.8×10^{-8} $(\mu g/m^3)^{-1}$ to 5.3×10^{-7} $(\mu g/m^3)^{-1}$ representing the uncertainty of this estimate. The EOIC document was published as Kirman et al. (2004) with the unit risk estimate recalculated as 4.5×10^{-8} $(\mu g/m^3)^{-1}$, with a range of values of 1.4×10^{-8} $(\mu g/m^3)^{-1}$ to 1.4×10^{-7} $(\mu g/m^3)^{-1}$.

The EOIC/Kirman et al. values are different from those in the current document because of the different assumptions inherent in the EOIC's approach and because the study used unpublished data from the two cohorts, which was necessary in order to combine the two data sets. A key difference is that EPA uses a linear model rather than a quadratic (dose-squared) model in the range of observation. Then, EPA uses a higher POD (1% extra risk), whereas Kirman et al. used a POD of 10^{-5} for their best estimate and a risk range of 10^{-4} to 10^{-6} for their range of values. The POD is not critical with a linear model, but with the quadratic model used by EOIC/Kirman et al., the lower the POD, the greater the impact of the quadratic model and the lower the resulting unit risk estimates.

In addition, EPA (1) includes all lymphohematopoietic tumor types likely to be caused by EtO and does not restrict the data to leukemia alone, (2) includes ages up to 85 years in the lifetable analysis rather than stopping at 70 years, (3) calculates unit risk estimates for cancer incidence as well as mortality, (4) uses a lower bound as the POD rather than the maximum likelihood estimate, and (5) uses the results of lagged analyses rather than unlagged analyses.

Another key difference is that the EOIC and Kirman et al. relied on earlier NIOSH results (Stayner et al., 1993), whereas EPA uses the results of NIOSH's more recent follow-up of the cohort (Steenland et al., 2004). Kirman et al. (2004) claim that a quadratic dose-response model provided the best fit to the data in the observable range and that this provides support for their assumed mode of action. However, the 2004 NIOSH data for lymphohematopoietic cancer in males suggest a supralinear exposure-response relationship (see Section 4.1.1.2 and Figure 4), which is inconsistent with a dose-squared model. Furthermore, EPA's review of the mode of action evidence does not support the mode of action assumed by EOIC/Kirman et al. (see Section 3.4).

4.4.2. Assessments Based on Laboratory Animal Studies

The California EPA summarized cancer potency factors for EtO as well as 118 other carcinogenic substances in a 1999 report (CalEPA, 1999). The EtO value is based on the incidence of mononuclear cell leukemia in female rats in the Snellings et al. (1984) rat bioassay because it was the most sensitive data set of all the sex, site, and species data sets available. The 95% upper bound value from a linear extrapolation procedure using these data gave a unit risk value of 8.8×10^{-5} $(\mu g/m^3)^{-1}$.

Health Canada (2001) based its carcinogenic hazard index value on the rodent data set with the lowest ED_{05} value of the data sets in Tables 1 through 3, which had a lower confidence limit of 1,500 μg/m^3. Using linear extrapolation, this is equivalent to an upper-bound risk of $0.05/1{,}500 = 3.3 \times 10^{-5}$ (μg/m^3)$^{-1}$. The human data then available were not used because Health Canada felt that the number of cases was relatively small and the uncertainty in the estimate was relatively large.

The EOIC (2001) and Kirman et al. (2004) also used linear and dose-squared extrapolation models to derive unit risk estimates based on the rat mononuclear cell leukemia data and the mouse lymphoma data. First, they used the multistage model to calculate the LEC_{10} (LEC_{01} for the male mouse lymphoma data) for the POD from the observable range. Then, using these PODs for linear extrapolation, Kirman et al. obtained a unit risk range of 3.9×10^{-6} (μg/m^3)$^{-1}$ to 1.5×10^{-5} (μg/m^3)$^{-1}$. Alternatively, Kirman et al. used a quadratic extrapolation model below the observable range to estimate secondary points of departure (LEC_{01}–LEC_{000001}; LEC_{001}–LEC_{000001} for the male mouse) for final linear low-dose extrapolation, yielding unit risks ranging from 2.6×10^{-8} (μg/m^3)$^{-1}$ to 4.9×10^{-6} (μg/m^3)$^{-1}$. These values are all smaller than the unit risks derived from the rodent data in this document and in the Health Canada document.

Another estimate was derived by Granath et al. (1999). They showed that the same rodent data that we have used here fit a multiplicative risk model but do not fit an additive risk model. They concluded from their multiplicative risk model that the doubling dose (the air concentration necessary to double the background incidence of tumors, a measure that is assumed to be the same for humans and rodents) is 22 ppm (95% confidence limits of 14–32 ppm) from the rat data and 19 (8–46) ppm from the mouse data. This is equivalent to a relative risk of approximately 2 per 20 ppm = 5.6×10^{-5} (μg/m^3)$^{-1}$. Using this relative risk and a background hematopoietic cancer lifetime risk of 1.8×10^{-2}, one obtains a unit risk of 1×10^{-6} (μg/m^3)$^{-1}$. This is 38 times smaller than the total cancer unit risk estimate derived from the laboratory animal data in this document and greater than 2 orders of magnitude smaller than the human estimate.

The multiplicative risk model has not been used in Agency carcinogen risk estimates that have been based on data from laboratory animals, because there is seldom a direct tumor site concordance between humans and rodents, and because the specific human tumor type must be specified for this method. Kuo et al. (2002) examined the difference between additive risk models and multiplicative risk models in predicting the results between mouse and rat data sets in the NTP database and found that in most cases the differences between the two models were smaller than the differences between chemical classes. Therefore, there is no compelling reason to use the multiplicative risk model with laboratory animal data in general or for the case of EtO specifically.

4.5. RISK ESTIMATES FOR OCCUPATIONAL EXPOSURES

The unit risk estimates derived in the preceding sections were developed for environmental exposure levels, where maximum modeled levels are on the order of 1-2 $\mu g/m^3$ (e-mail dated October 3, 2005, from Mark Morris, U.S. EPA, to Jennifer Jinot, U.S. EPA), and are not applicable to occupational exposures. However, occupational exposure levels are of concern to EPA when EtO is used as a pesticide (e.g., fumigant for spices). Therefore, extra risk estimates were calculated for a number of occupational exposure scenarios. For these occupational scenarios, exposure-response models from the NIOSH cohort were used in conjunction with the life-table program, as previously discussed in Section 4.1. A 35-year exposure occurring between ages 20 and 55 years was assumed, and exposure levels ranging from 0.1 to 1 ppm 8-hour TWA were examined (i.e., ranging from about 1,300 to 13,000 ppm × days).

For lymphohematopoietic cancer mortality in males, the best-fitting (natural) log cumulative exposure Cox regression model (Steenland et al., 2004; see also Section 4.1.1.2), lagged 15 years, was used. For lymphohematopoietic cancer incidence in males, the exposure-response relationship was assumed to be the same as for mortality (see Section 4.1.1.3). The extra risk results for lymphohematopoietic cancer mortality and incidence in males are presented in Table 20. As can be seen in Table 20, the extra risks for these occupational exposure levels are in the "plateau" region of the exposure-response relationships and increase less than proportionately with exposure. [For occupational exposures less than about 1,000 ppm × days, or about 0.08 ppm 8-hour TWA for 35 years, risk estimates are no longer in the plateau region (see Figure 4) but rather in a region of greater uncertainty for the log cumulative exposure model, and one might want to use the linear regression of the categorical results that was used for environmental exposures (see Section 4.1.1.2). Furthermore, if one is using the linear model in this range and also estimating risks for exposure levels in the range between about 0.08 and 0.5 ppm (or where the linear and log cumulative exposure Cox regression models meet) 8-hour TWA, one might want to use the linear model for the entire range up to 0.5 ppm 8-hour TWA to avoid a discontinuity between the two models; thus, results for the linear model for exposure levels up to 0.5 ppm 8-hour TWA are also presented in Table 20. While the best-fitting model would generally be preferred in the 0.08 and 0.5 ppm 8-hour TWA exposure range, there is model uncertainty, so the use of either model could be justified. For exposures higher than where the linear and log cumulative exposure Cox regression models meet, the log cumulative exposure model exclusively is recommended.]

For breast cancer mortality, the best-fitting (natural) log cumulative exposure Cox regression model (Steenland et al., 2004; see also Section 4.1.2.2), lagged 20 years, was used.

The breast cancer mortality risk estimates are presented merely for comparison; the breast cancer incidence risk estimates are preferred because incidence estimates are the objective, and because the incidence risk estimates are based on more cases and the incidence data (for the subcohort with interviews) are adjusted for a number of breast cancer risk factors (see Section 4.1.2.3). In terms of the incidence data, the subcohort data are preferred to the full cohort data because the subcohort data are adjusted for these potential confounders and also because the full cohort data suffer from incomplete ascertainment of breast cancer cases. For breast cancer incidence in the subcohort with interviews, a number of Cox regression exposure-response models fit almost equally well (Steenland et al., 2003; see also Section 4.1.2.3 and Table 13). These include a log cumulative exposure model and a cumulative exposure model, both with a 15-year lag, and a log cumulative exposure model with no lag. Steenland et al. (2003) also provide a duration of exposure model with a marginally better fit; however, models using duration of exposure are less useful for estimating exposure-related risks, and duration of exposure and cumulative exposure are correlated, thus, only the cumulative exposure models are considered here.

The extra risk results for breast cancer incidence in females from the cumulative exposure models listed above are presented in Table 21. Of these cumulative exposure models, the lagged models are preferred because the inclusion of a 15-year lag for the development of breast cancer seems more biologically realistic than not including a lag. As can be seen in Table 21, the extra risk estimates for the lagged log cumulative and cumulative exposure models differ substantially. Furthermore, the categorical results for breast cancer incidence in the subcohort with interviews suggest that, for the lowest four exposure quintiles, the log cumulative exposure model overestimates the RR, while the cumulative exposure model generally underestimates the RR, with the categorical results largely falling between the RR estimates of those two models (see Figure 8). [The lowest four exposure quintiles represent individual worker exposures ranging from 0 to about 15,000 ppm × days, which covers the range of cumulative exposures for the occupational exposure scenarios of interest in this assessment.] Therefore, the linear regression of the categorical results for the lowest four exposure quintiles in the subcohort with interviews was again used (see Section 4.1.2.3). Extra risk estimates using this linear regression model are also presented in Table 21 and are the preferred estimates because, in the absence of a clearer "best-fitting" model for the continuous data, the linear regression best represents the categorical RR results for exposures below about 15,000 ppm × days. [For occupational exposures above this level, the Steenland et al. log cumulative exposure Cox regression model (with a 15-year lag), which additionally reflects the highest exposure quintile, would be preferred; however, for estimating risks from future exposures, such high cumulative exposures are unlikely to occur because the current Occupational Safety and Health Administration Permissible Exposure Limit is 1 ppm (8-hour TWA).]

Extra risk estimates for a 45-year exposure to the same exposure levels were nearly identical to those from the 35-year exposure for both lymphohematopoietic cancer in males and breast cancer in females (results not shown). With the 15-year lag, the assumption of an additional 10 years of exposure only negligibly affects the risks above age 70 and has little impact on lifetime risk. For exposure scenarios of 35-45 years but with 8-hour TWAs falling between those presented in the Tables, one can estimate the extra risk by interpolation. For exposure scenarios with durations of exposure less than 30-35 years, one could roughly estimate extra risk by calculating the cumulative exposure and finding the extra risk for a similar cumulative exposure in Table 20 (or 21). For a more precise estimation, or for exposure scenarios of much shorter duration or for specific age groups, one should do the calculation using the lifetable presented in Appendix C.

Table 1. Tumor incidence data in National Toxicology Program Study of B6C3F$_1$ mice (NTP, 1987)[a]

Gender/tumor type	EtO concentration (time-weighted average)[b] 0 ppm	50 ppm (16.3 mg/m^3)	100 ppm (32.7 mg/m^3)	EC_{10} (LEC_{10})[c], [mg/m^3]	Unit risk (0.1/LEC_{10}) [per mg/m^3]
Males					
Lung adenomas plus carcinomas	11/49	19/49***	26/49***	6.94 (4.51)	2.22×10^{-2}
Females					
Lung adenomas plus carcinomas	2/44	5/44	22/49***	14.8 (9.12)	1.1×10^{-2}
Malignant lymphoma	9/44	6/44	22/49*	21.1 (13.9)	7.18×10^{-3}
Uterine carcinoma	0/44	1/44	5/49*	32.8 (23.1)	4.33×10^{-3}
Mammary carcinoma[d]	1/44	8/44*	6/49	9.69 (5.35)	1.87×10^{-2}

[a] Incidence data were adjusted by eliminating the animals that died prior to the occurrence of the first tumor or prior to 52 weeks, whichever was earlier.

[b] Adjusted to continuous exposure from experimental exposure conditions of 6 hours/day, 5 days/week; 1 ppm = 1.83 mg/m^3.

[c] Calculated using Tox_Risk program.

[d] Highest dose was deleted while fitting the dose-response data.

*p<0.05 (pairwise Fisher's exact test).
**p<0.01 (pairwise Fisher's exact test).
***p<0.001 (pairwise Fisher's exact test).

Table 2. Tumor incidence data in Lynch et al. (1982, 1984) study of male F344 rats

Tumor type	Concentration (time-weighted average)[a]			EC_{10} (LEC_{10})[b], [mg/m^3]	Unit risk ($0.1/LEC_{10}$) [per mg/m^3]
	0 ppm	50 ppm (19.1 mg/m^3)	100 ppm (38.1 mg/m^3)		
Splenic mononuclear cell leukemia[c]	24/77	38/79*	30/76	7.11 (3.94)	2.54×10^{-2}
Testicular peritoneal mesothelioma	3/78	9/79	21/79**	16.7 (11.8)	8.5×10^{-3}
Brain mixed-cell glioma	0/76	2/77	5/79**	65.7 (37.4)	2.68×10^{-3}

[a] Adjusted to continuous exposure from experimental exposure conditions of 7 hours/day, 5 days/week; 1 ppm = 1.83 mg/m^3.
[b] Calculated using Tox_Risk program.
[c] Highest dose deleted while fitting the dose-response data.

*$p<0.05$ (pairwise Fisher's exact test).
**$p<0.01$ (pairwise Fisher's exact test).

Table 3. Tumor incidence data in Snellings et al. (1984) and Garman et al. (1985) reports on F344 rats[a]

Gender/tumor type	Concentration (time-weighted average)[b] 0 ppm[d]	10 ppm (3.27 mg/m^3)	33 ppm (10.8 mg/m^3)	100 ppm (32.7 mg/m^3)	EC_{10} (LEC_{10})[c] [mg/m^3]	Unit risk (0.1/LEC_{10}) [per mg/m^3]
Males						
Splenic mononuclear cell leukemia	13/97 (13%)[e]	9/51 (18%)	12/39* (32%)	9/30* (30%)	12.3 (6.43)	1.56×10^{-2}
Testicular peritoneal mesothelioma	2/97 (21%)	2/51 (3.9%)	4/39 (10%)	4/30* (13%)	22.3 (11.6)	8.66×10^{-3}
Primary brain tumors	1/181 (0.55%)	1/92 (1.1%)	5/85* (5.9%)	7/87** (8.1%)	36.1 (22.3)	4.5×10^{-3}
Females						
Splenic mononuclear cell leukemia	11/116 (9.5%)	11/54* (21%)	14/48** (30%)	15/26*** (58%)	4.46 (3.1)	3.23×10^{-2}
Primary brain tumors	1/188 (0.53%)	1/94 (1.1%)	3/92 (3.3%)	4/80* (5%)	63.8 (32.6)	3.07×10^{-3}

[a] Denominators refer to the number of animals for which histopathological diagnosis was performed. For brain tumors Garman et al. (1985) included animals in the 18-month and the 24-month sacrifice and found dead or euthanized moribund of those alive at the time of the first brain tumor, whereas for the other sites Snellings et al. (1984) included animals only at the 24-month sacrifice.

[b] Adjusted to continuous exposure from experimental exposure conditions of 6 hours/day, 5 days/week; 1 ppm = 1.83 mg/m^3.

[c] Using Tox_Risk program.

[d] Results for both control groups combined.

[e] Numbers in parentheses indicate percent incidence values.

* $p<0.05$ (pairwise Fisher's exact test).
** $p<0.01$ (pairwise Fisher's exact test).
*** $p<0.001$ (pairwise Fisher's exact test).

Table 4. Cytogenetic effects in humans

Number exposed (number of controls)	Exposure time (years)		Ethylene oxide level in air (ppm)[a]		Cytogenetic observations			Reference
	Range	Mean	Range	Mean (TWA)	CA	SCE	MN	
33 (0)	1–14		±0.05–8	±0.01[b]	(+)			Clare et al. (1985)
Site I: 13 Site II: 22 Site III: 25–26 (171 total)			0.5[c] 5–10[c] 5–20[c]		– – +	– + +		Stolley et al. (1984); Galloway et al. (1986)
12 (12)			±36			+		Garry et al. (1979)
14 (14)			<0.07–4.3[c]			–		Hansen et al. (1984)
Factory I: 18 Factory II: l0 (20 total)	0.5–8 0.5–8	3.2 1.7		<1 <1	+ +	– –	+[d]	Hogstedt et al. (1983)
15 smokers (7) 10 nonsmokers (15)	0.5–10 0.5–10	5.7 4.5	20–123 20–123			+ +		Laurent et al. (1984)
10 (10)		3	60–69[c]		+	+		Lerda and Rizzi (1992)
Low dose: 9 (48) High dose: 27 (10)		4 15	2.7–10.9 2.7–82	2.7 5.5	+ +	– +		Major et al. (1996)
34 (23)		8[e]	<0.1–2.4[c]	<0.3	–	+	–	Mayer et al. (1991)
11 smokers 14 nonsmokers (10 total)			0.5–4l7[f] 0.5–208[f]			– –		Popp et al. (1994)
75 (22)	3–14	7	2–5[c]		+		+	Ribeiro et al. (1994)
56 (141)	1–10		1–40[c]		+	+		Richmond et al. (1985)
22 (22) 19 (19)	0.6–4 1.5–15	3 6.8	0.2–0.5[c] 3.7–20[c]	0.35 10.7	(+) +	+ +		Sarto et al. (1984)
10 (10)			0–9.3[c]	1.84		+		Sarto et al. (1987)

Table 4. Cytogenetic effects in humans (continued)

Number exposed (number of controls)	Exposure time (years)		Ethylene oxide level in air (ppm)[a]		Cytogenetic observations			Reference
	Range	Mean	Range	Mean (TWA)	CA	SCE	MN	
9 3 (27 total)	0.5–12	5	0.025–0.38[c] >0.38[g]				– +[h]	Sarto et al. (1990)
5 5 (10 total)	0.1–4 4–12	2 8.6	<1–4.4	0.025 0.38		– +	–[I] –[I]	Sarto et al. (1991)
32 11 (8 total)		5.1 9.5	0–0.3[c] 0.1 3–0.3[c]	0.04 0.16		+ +	– –	Schulte et al. (1992)
9 hospital workers (8) 15 factory workers (15)	2–6 3–27	4 12	20–25 17–33		+ +	+ +	– +	Tates et al. (1991)
7 7 7 (7 total)	Accidental <5 >15		28–429[c] <0.005–0.02 <0.005–0.01			– – –	– – –	Tates et al. (1995)
Low exposure: 9 High exposure: 5 (13 total)				13[j] 501[j]		– +		Yager et al. (1983)
19 17 (35 total)	1–5 6–14		<0.05–8 <0.05–8	<0.05 <0.05	– –			van Sittert et al. 1985

Table 4. Cytogenetic effects in humans (continued)

[a] 1 ppm = 1.83 mg ethylene oxide/m^3.
[b] Calculated by linear extrapolation.
[c] TWA (8-hour).
[d] Positive for erythroblasts and polychromatic erythrocytes (negative for lymphocytes).
[e] Maximum years exposed.
[f] Peak concentrations.
[g] Exposed acutely from sterilizer leakage in addition to chronic exposure.
[h] Nasal mucosa.
[I] Buccal cells.
[j] Average 6-month cumulative exposure (mg).

CA = chromosomal aberrations
MN = micronucleus
SCE = sister chromatid exchange
TWA = time-weighted average

Table 5. Cox regression results for all lymphohematopoietic cancer mortality in males[a]

Exposure variable[b]	*p* value	Coefficient (SE)	ORs by category[c] (95% CI)
Cumulative exposure	0.12	0.0000040 (0.0000022)	
Log cumulative exposure, 15-year lag	0.02	0.119 (0.052)	
Categorical cumulative exposure, 15-year lag	0.15		1.00, 1.23 (0.32–4.73), 2.52 (0.69–9.22), 3.13 (0.95–10.37), 3.42 (1.09–10.73)

[a] Based on 37 cases.
[b] Cumulative exposure is in ppm × days.
[c] Exposure categories are 0, >0–1,199, 1,200–3,679, 3,680–13,499, ≥13,500 ppm × days.

Source: Steenland et al. (2004), Table 6.

Table 6. Extra risk estimates for all lymphohematopoietic cancer mortality in males from various levels of lifetime exposure to ethylene oxide

Exposure concentration (ppm)	Extra risk			95% UCL on extra risk
	Continuous log cumulative exposure model[a]	Continuous cumulative exposure model	Categorical cumulative exposure model[b]	
0.0001	4.70×10^{-3}	6.22×10^{-7}	4.22×10^{-5}	9.25×10^{-5}
0.001	1.24×10^{-2}	6.22×10^{-6}	4.22×10^{-4}	9.25×10^{-4}
0.01	2.25×10^{-2}	6.23×10^{-5}	4.21×10^{-3}	9.19×10^{-3}
0.1	3.55×10^{-2}	6.32×10^{-4}	--	--
1	5.22×10^{-2}	7.28×10^{-3}	--	--
10	7.36×10^{-2}	3.34×10^{-1}	--	--

[a] With 15-year lag.
[b] From linear regression of categorical results as described in text. The linear regression model is intended for low exposures; therefore, results for 0.1 ppm lifetime exposure and greater are not presented.

Table 7. EC_{01}, LEC_{01}, and unit risk estimates for lymphohematopoietic cancer in males[a]

Model[b]	Incidence			Mortality		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	unit risk (per ppm)
Cumulative exposure, 0 lag	0.784	0.412	2.43×10^{-2}	1.31	0.686	1.46×10^{-2}
Log cumulative exposure, 15-year lag	0.000130	0.0000570	175.4	0.000517	0.000124	80.6
Categorical[c]; cumulative exposure, 15-year lag	0.0133	0.00608	**1.64**	0.0238	0.0109	0.917

[a] From lifetime continuous exposure. Unit risk = $0.01/LEC_{01}$.
[b] From Steenland et al. (2004), Table 6, Cox regression models.
[c] Regression coefficient derived from linear regression of categorical results, dropping the highest exposure group, as described in Section 4.1.1.2.

Table 8. Cox regression results for "lymphoid" cancer mortality in males[a]

Exposure variable[b]	*p* value	Coefficient (SE)	ORs by category[c] (95% CI)
Cumulative exposure	0.06	0.0000050 (0.0000022)	
Log cumulative exposure, 15-year lag	0.02	0.138 (0.061)	
Categorical cumulative exposure, 15-year lag	0.13		1.00, 0.90 (0.16–5.24), 2.89 (0.65–12.86), 2.74 (0.65–11.55), 3.76 (1.03–13.64)

[a] Based on 27 cases of NHL, myeloma, and lymphocytic leukemia.
[b] Cumulative exposure is in ppm × days.
[c] Exposure categories are 0, >0–1,199, 1,200–3,679, 3,680–13,499, ≥13,500 ppm × days.

Source: Steenland et al. (2004), Table 7.

Table 9. EC_{01}, LEC_{01}, and unit risk estimates for "lymphoid" cancer in males[a,b]

Model[c]	Incidence			Mortality		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	unit risk (per ppm)
Cumulative exposure, 0 lag	0.796	0.462	2.16×10^{-2}	1.39	0.809	1.24×10^{-2}
Log cumulative exposure, 15-year lag	0.000154	0.0000620	161.3	0.000885	0.000166	60.2
Categorical[d]; cumulative exposure, 15-year lag	0.0216	0.00836	1.20	0.0427	0.0165	0.606

[a] From lifetime continuous exposure. Unit risk = $0.01/LEC_{01}$.
[b] "Lymphoid" cancers include NHL, myeloma, and lymphocytic leukemia.
[c] From Steenland et al. (2004), Table 7, Cox regression models.
[d] Regression coefficient derived from linear regression of categorical results, dropping the highest exposure group, as described in Section 4.1.1.2.

Table 10. Cox regression results for breast cancer mortality in females[a]

Exposure variable[b]	*p* value	Coefficient (SE)	ORs by category[c] (95% CI)
Cumulative exposure	0.34	0.0000049 (0.0000048)	
Log cumulative exposure, 20-year lag	0.01	0.084 (0.035)	
Categorical cumulative exposure, 20-year lag	0.07		1.00, 1.76 (0.91–3.43), 1.77 (0.88–3.56), 1.97 (0.94–4.06), 3.13 (1.42–6.92)

[a] Based on 103 cases of breast cancer (ICD-9 174,175).
[b] Cumulative exposure is in ppm × days.
[c] Exposure categories are 0, >0–646, 647–2,779, 2,780–12,321, ≥12,322 ppm × days.

Source: Steenland et al. (2004), Table 8.

Table 11. Extra risk estimates for breast cancer mortality in females from various levels of lifetime exposure to ethylene oxide

Exposure concentration (ppm)	Extra risk		95% UCL on extra risk
	Continuous log cumulative exposure model[a]	Categorical cumulative exposure model[a,b]	
0.0001	3.60×10^{-3}	2.60×10^{-5}	5.15×10^{-5}
0.001	9.66×10^{-3}	2.60×10^{-4}	5.15×10^{-4}
0.01	1.70×10^{-2}	2.60×10^{-3}	5.14×10^{-3}
0.1	2.57×10^{-2}	--	--
1	3.63×10^{-2}	--	--
10	4.89×10^{-2}	--	--

[a] With 20-year lag.
[b] From linear regression of categorical results as described in text. The linear regression model is intended for low exposures; therefore, results for 0.1 ppm lifetime exposure and greater are not presented.

Table 12. EC_{01}, LEC_{01}, and unit risk estimates for breast cancer mortality in females[a]

Model[b]	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Log cumulative exposure, 20-year lag	0.00112	0.000219	45.7
Categorical[c]; cumulative exposure, 20-year lag	0.0387	0.0195	0.513

[a] From lifetime continuous exposure. Unit risk = $0.01/LEC_{01}$.
[b] From Steenland et al. (2004), Table 8, Cox regression models.
[c] Regression coefficient derived from linear regression of categorical results, as described in Section 4.1.2.2.

Table 13. Cox regression results for breast cancer incidence in females[a,b]

Cohort	Exposure variable[c]	Coefficient (SE), *p* value	ORs by category[d] (95% CI)
Full incidence study cohort n = 7,576 319 cases	Cumulative exposure, 15-year lag	0.0000054 (0.0000035), *p*=0.12	
	Log cumulative exposure, 15-year lag	0.037 (0.019), *p*= 0.05	
	Categorical cumulative exposure, 15-year lag		1.00, 1.07 (0.72–1.59), 1.00 (0.67–1.50), 1.24 (0.85–1.90), 1.17 (0.78–1.78), 1.74 (1.16–2.65)
Subcohort with interviews n = 5,139 233 cases	Cumulative exposure, 15-year lag	0.0000095 (0.0000041), *p*= 0.02	
	Log cumulative exposure, 15-year lag	0.050 (0.023), *p*=0.03	
	Categorical cumulative exposure, 15-year lag		1.00, 1.06 (0.66–1.71), 0.99 (0.61–1.60), 1.24 (0.76–2.00), 1.42 (0.88–2.29), 1.87 (1.12–3.10)

[a] Invasive breast cancer (ICD-9 174) and carcinoma in situ (ICD-9 233.0).
[b] Cases and controls matched on age and race (white/nonwhite). Full cohort models include cumulative exposure and categorical variable for year of birth (quartiles). Subcohort models include cumulative exposure, categorical variables for year of birth (quartiles), breast cancer in first-degree relative, and parity.
[c] Cumulative exposure is in ppm × days.
[d] Exposure categories are 0, >0–647, 647–2,026, 2,026–4,919, 4,919–14,620, >14,620 ppm × days.

Source: Steenland et al. (2003), Tables 4 and 5.

Table 14. EC_{01}, LEC_{01}, and unit risk estimates for breast cancer incidence in females - invasive and in situ[a]

Model[b]	With interviews			Full cohort		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Cumulative exposure, 15-year lag	0.125	0.0732	0.137	0.220	0.107	9.35×10^{-2}
Log cumulative exposure, 15-year lag	0.0000693	0.0000399	251	0.000108	0.0000492	203
Categorical[c]; cumulative exposure, 15-year lag	0.0238	0.0110	**0.909**	0.0466	0.0174	0.575

[a] All-cause mortality adjusted (to dying of something other than breast cancer or developing breast cancer). Unit risk = $0.01/LEC_{01}$.
[b] From Steenland et al. (2003), Tables 4 and 5, Cox regression models.
[c] Regression coefficient derived from linear regression of categorical results, as described in Section 4.1.2.3.

Table 15. EC_{01}, LEC_{01}, and unit risk estimates for breast cancer incidence in females - invasive only[a]

Model[b]	With interviews			Full cohort		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Cumulative exposure, 15-year lag	0.150	0.0875	0.114	0.263	0.127	7.87×10^{-2}
Log cumulative exposure, 15-year lag	0.0000894	0.0000460	217	0.000153	0.0000593	169
Categorical[c]; cumulative exposure, 15-year lag	0.0287	0.0132	0.758	0.0561	0.0210	0.476

[a] All-cause mortality adjusted (to dying of something other than breast cancer or developing breast cancer). Unit risk = $0.01/LEC_{01}$.
[b] From Steenland et al. (2003), Tables 4 and 5, Cox regression models.
[c] Regression coefficient derived from linear regression of categorical results, as described in Section 4.1.2.3.

Table 16. Upper-bound unit risks (per μg/m^3) obtained by combining tumor sites

Combination method[a]	NTP (1987) female mouse	Lynch et al. (1982, 1984) male rat	Snellings et al. (1984)[b]	
			Male rat	Female rat
U.c.b. on sum of risks[c]	2.71×10^{-5}	4.17×10^{-5}	2.19×10^{-5}	3.37×10^{-5}
Sum of unit risks[d]	4.12×10^{-5}	3.66×10^{-5}	2.88×10^{-5}	3.54×10^{-5}
Time-to-tumor analysis and u.c.b on sum of risks[c]	4.55×10^{-5}	–	–	–

[a] Unit risk in these methods is the slope of the straight line extrapolation from a point of departure at the dose corresponding to a value of 0.1 for the 95% upper confidence bound on total extra risk.
[b] Includes data on brain tumors from the analysis by Garman et al. (1985). See Table 3.
[c] U.c.b. = 95% upper confidence bound. At a given dose, the maximum likelihood estimate (MLE) of the combined extra risk was determined by summing the MLE of risk due to each tumor type. The variance associated with this value was determined by summing over the variances due to each tumor type.
[d] Sum of values in last column of Tables 1 through 3.

Table 17. Unit risk values from multistage Weibull[a] time-to-tumor modeling of mouse tumor incidence in the NTP (1987) study

Tumor type	Unit risk, $0.1/LEC_{10}$ (per $\mu g/m^3$) from time to tumor analysis	Unit risk, $0.1/LEC_{10}$ (per $\mu g/m^3$) (Table 1)[b]	Ratio of unit risks time-to-tumor/ grouped data
Males			
Lung: alveolar/bronchiolar adenoma and carcinoma	3.01×10^{-5}	2.22×10^{-5}	1.4
Females			
Lung: alveolar/bronchiolar adenoma and carcinoma	2.40×10^{-5}	1.10×10^{-5}	2.2
Malignant lymphoma	1.43×10^{-5}	7.18×10^{-6}	2.0
Uterine carcinoma	6.69×10^{-6}	4.33×10^{-6}	1.5
Mammary carcinoma	8.69×10^{-6}	1.87×10^{-5}	0.5

[a] $P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$, where d is inhaled ethylene oxide concentration in ppm, t is weeks until death with tumor. In all cases, k = 1 provided the optimal model.

[b] Incidence data modeled using multistage model without taking time to tumor into account.

Table 18. Summary of unit risk estimates (per μg/m^3) in animal bioassays

Assay	Males	Females
NTP (1987), B6C3F$_1$ mice	3.01×10^{-5} [a]	4.55×10^{-5} [b]
Lynch et al. (1982, 1984), F344 rats	3.66×10^{-5} [c]	–
Snellings et al. (1984), F344 rats	2.19×10^{-5} [d]	3.37×10^{-5} [d]

[a] From time-to-tumor analysis of lung adenomas and carcinomas, Table 17.
[b] Upper bound on sum of risks from the time-to-tumor analysis of the NTP data, Table 16.
[c] Sum of (upper bound) unit risks (see text for explanation), Table 16.
[d] Upper bound on sum of risks, Table 16.

Table 19. Comparison of unit risk estimates

Assessments	Data source	Inhalation unit risk estimate[a]
Based on human data		
U.S. EPA (this document)	Lymphohematopoietic cancer incidence in sterilizer workers (NIOSH)[b]	9.0×10^{-4} $(\mu g/m^3)^{-1}$
	Breast cancer incidence in sterilizer workers (NIOSH)[c]	5.0×10^{-4} $(\mu g/m^3)^{-1}$
Ethylene Oxide Industry Council (Kirman et al., 2004)	Leukemia mortality in combined NIOSH and UCC cohorts	4.5×10^{-8} $(\mu g/m^3)^{-1}$ Range of 1.4×10^{-8} $(\mu g/m^3)^{-1}$ to 1.4×10^{-7} $(\mu g/m^3)^{-1}$ [d]
Based on rodent data		
U.S. EPA (this document)	Female mouse tumors	4.6×10^{-5} $(\mu g/m^3)^{-1}$
California EPA (CalEPA, 1999)	Mononuclear cell leukemia in female rats	8.8×10^{-5} $(\mu g/m^3)^{-1}$
Health Canada (Health Canada, 2001)[e]	Mononuclear cell leukemia in female rats	3.3×10^{-5} $(\mu g/m^3)^{-1}$
Ethylene Oxide Industry Council (Kirman et al., 2004)	Mononuclear cell leukemia in rats and lymphomas in mice	Range of 2.6×10^{-8} $(\mu g/m^3)^{-1}$ to 1.5×10^{-5} $(\mu g/m^3)^{-1}$ [f]
Granath et al. (1999)	Pooled data from all tumor sites using multiplicative model; used doubling concentration in rodents and human background risk of all hematopoietic cancers	1.2×10^{-6} $(\mu g/m^3)^{-1}$

[a] Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, EPA believes increased early-life susceptibility should be assumed in the absence of chemical-specific data. If estimating a unit risk for a constant lifetime exposure for ages 0–70 years, EPA would apply ADAFs to the potency estimate of 9.0×10^{-4} $(\mu g/m^3)^{-1}$ to obtain a full lifetime unit risk estimate of 1.5×10^{-3} $(\mu g/m^3)^{-1}$, in accordance with EPA's Supplemental Guidance (U.S. EPA, 2005b). Other EPA estimates in this table and the footnotes are not the final estimates recommended in this assessment and are left unadjusted for early-life susceptibility. The non-EPA estimates in the table are shown as reported and do not account for potential increased early-life susceptibility for lifetime exposures that include childhood.

[b] Estimate based on lymphohematopoietic cancer mortality is 5.0×10^{-4} $(\mu g/m^3)^{-1}$.

[c] Estimate based on breast cancer mortality is 2.8×10^{-4} $(\mu g/m^3)^{-1}$.

[d] Estimates based on linear extrapolation from EC0001 - EC000001 obtained from the quadratic model.

[e] WHO (2003) presents the same quantitative risk estimates for cancer as Health Canada (2001), Health Canada having provided the first draft of WHO's assessment.

[f] Estimates based on quadratic extrapolation model below the observable range of the data (i.e., below the LEC10 or LEC01 obtained using multistage model) with various points of departure (LEC01 - LEC000001) for final linear extrapolation (see Section 4.4.2).

Table 20. Extra risk estimates for lymphohematopoietic cancer in males for various occupational exposure levels[a]

8-hour TWA (ppm)	Lymphohematopoietic cancer mortality				Lymphohematopoietic cancer incidence[d]			
	log cumulative exposure Cox regression model[b]		linear model[c]		log cumulative exposure Cox regression model[b]		linear model[c]	
	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL
0.1	0.025	0.060	0.0077	0.017	0.046	0.11	0.013	0.029
0.2	0.029	0.071	0.015	0.033	0.052	0.13	0.027	0.057
0.3	0.031	0.078	0.022	0.049	0.056	0.14	0.040	0.084
0.4	0.033	0.084	0.030	0.064	0.060	0.15	0.052	0.11
0.5	0.034	0.088	0.038	0.079	0.062	0.16	0.065	0.13
0.6	0.035	0.092		0.11	0.064	0.16		0.16
0.7	0.036	0.095			0.066	0.17		
0.8	0.037	0.098			0.067	0.17		
0.9	0.038	0.10			0.069	0.18		
1.0	0.039	0.10			0.070	0.18		

[a] Assuming a 35-year exposure between ages 20 and 55 years (see Section 4.6).

[b] From the best-fitting (natural) log cumulative exposure Cox regression model for lymphohematopoietic cancer mortality in males; 15-year lag (Steenland et al., 2004; see also Section 4.1.1.2).

[c] Linear regression of categorical results (see Section 4.1.1.2); extra risk estimates from the linear model are provided only up to the exposure level where the linear model meets the log cumulative exposure Cox regression model

[d] Assumes same exposure-response relationship as for lymphohematopoietic cancer mortality.

Table 21. Extra risk estimates for breast cancer in females for various occupational exposure levels[a]

8-hour TWA (ppm)	Breast cancer mortality		Breast cancer incidence[c]							
	log cumulative exposure model[b] (20-year lag)		log cumulative exposure model (15-year lag)		log cumulative exposure model (no lag)		cumulative exposure model (15-year lag)		linear regression model[d] (15-year lag)	
	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL
0.1	0.018	0.038	0.059	0.11	0.13	0.27	0.0014	0.0024	0.0075	**0.016**
0.2	0.021	0.044	0.066	0.13	0.15	0.31	0.0028	0.0048	0.015	**0.032**
0.3	0.022	0.048	0.070	0.14	0.16	0.33	0.0042	0.0072	0.022	**0.048**
0.4	0.024	0.051	0.073	0.15	0.16	0.35	0.0056	0.0097	0.029	**0.063**
0.5	0.024	0.053	0.075	0.15	0.17	0.36	0.0070	0.012	0.037	**0.078**
0.6	0.025	0.055	0.077	0.15	0.17	0.37	0.0085	0.015	0.044	**0.092**
0.7	0.026	0.057	0.079	0.16	0.18	0.38	0.0099	0.017	0.051	**0.11**
0.8	0.026	0.059	0.080	0.16	0.18	0.39	0.011	0.020	0.058	**0.12**
0.9	0.027	0.060	0.082	0.16	0.18	0.39	0.013	0.023	0.065	**0.13**
1.0	0.027	0.061	0.083	0.17	0.19	0.40	0.014	0.025	0.072	**0.15**

[a] Assuming a 35-year exposure between ages 20 and 55 years.
[b] Best-fitting (natural) log cumulative exposure Cox regression model for breast cancer mortality in females (Steenland et al., 2004).
[c] From incidence data for subcohort with interviews; invasive and in situ tumors (Steenland et al., 2003).
[d] Regression coefficient derived from linear regression of categorical results, excluding the highest exposure group, as described in Section 4.1.2.3.

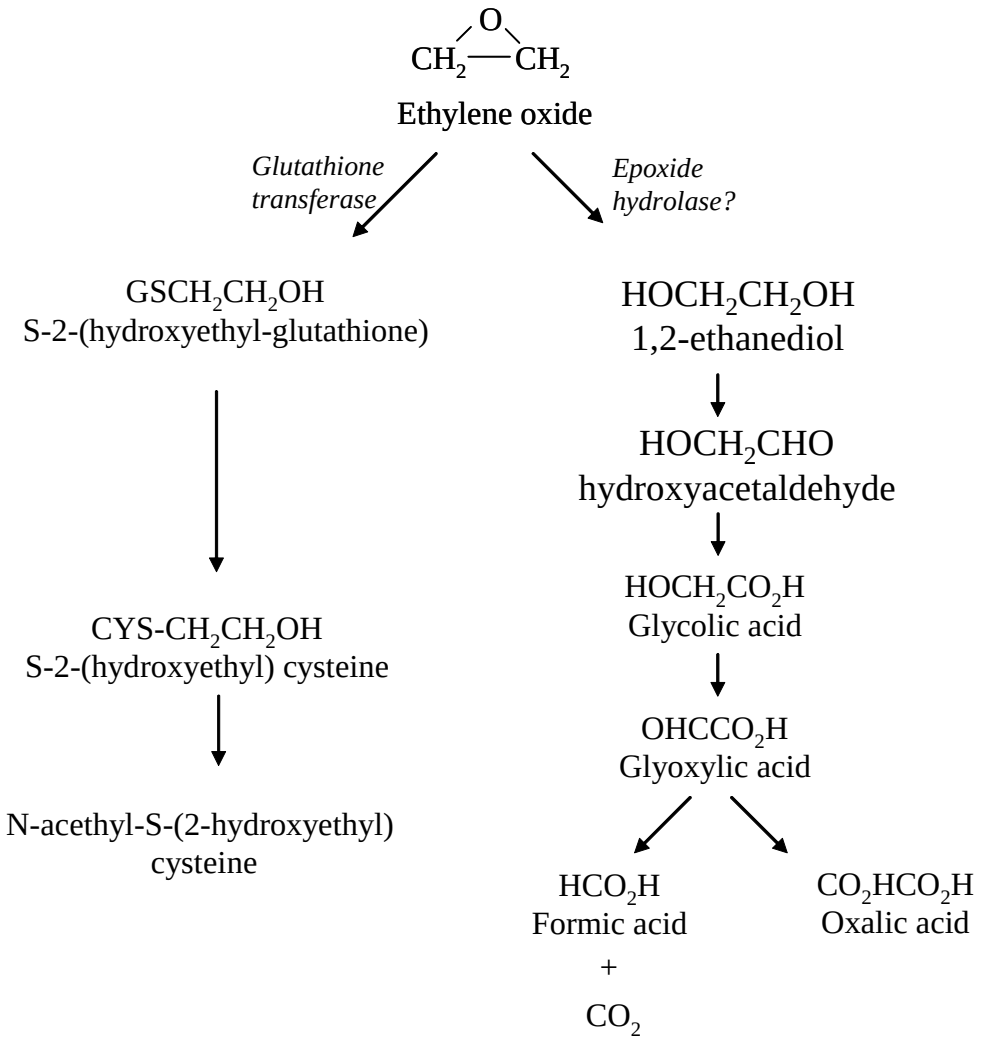

Figure 1. Metabolism of ethylene oxide

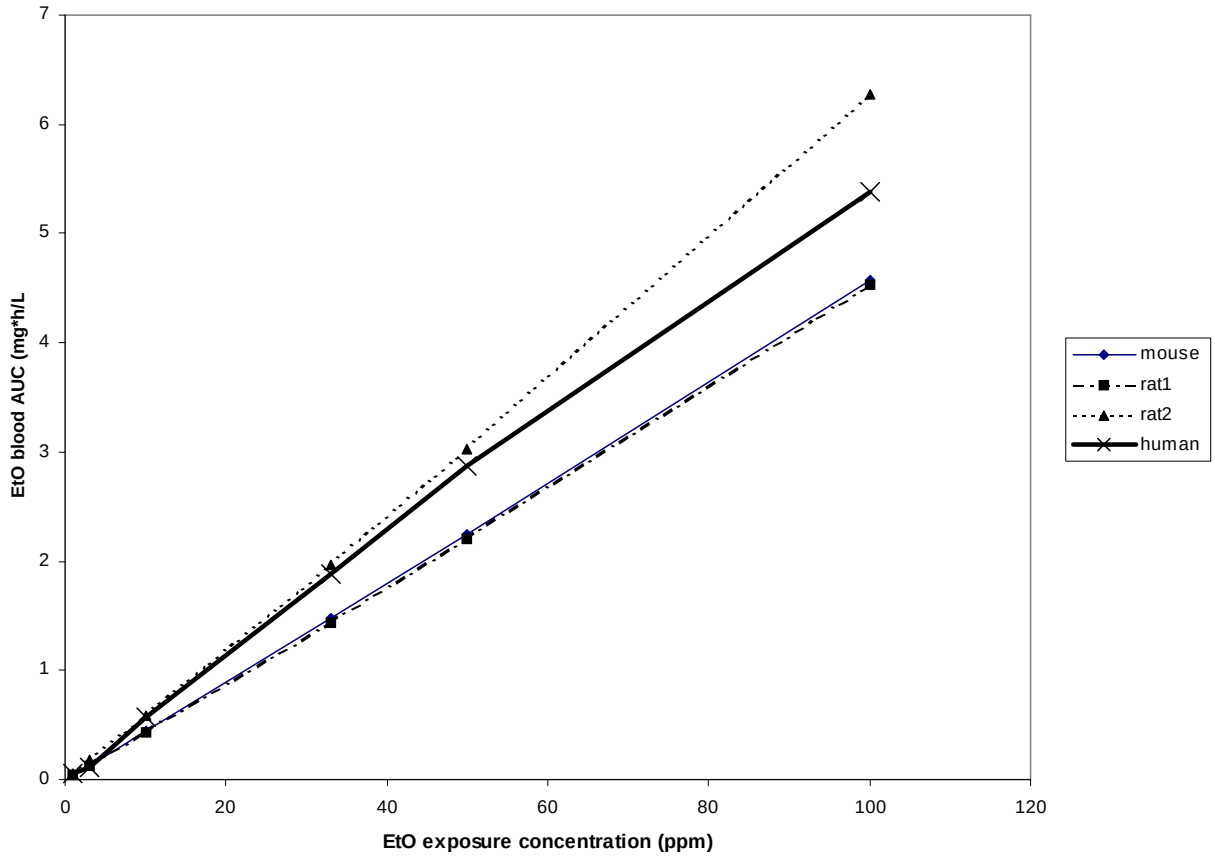

Figure 2. Simulated blood AUCs for EtO following a 6-hour exposure to EtO from the rat, mouse, and human PBPK models of Fennell and Brown (2001); based on data presented in Fennell and Brown (2001). (Rat1 and rat2 results use different values for pulmonary uptake.)

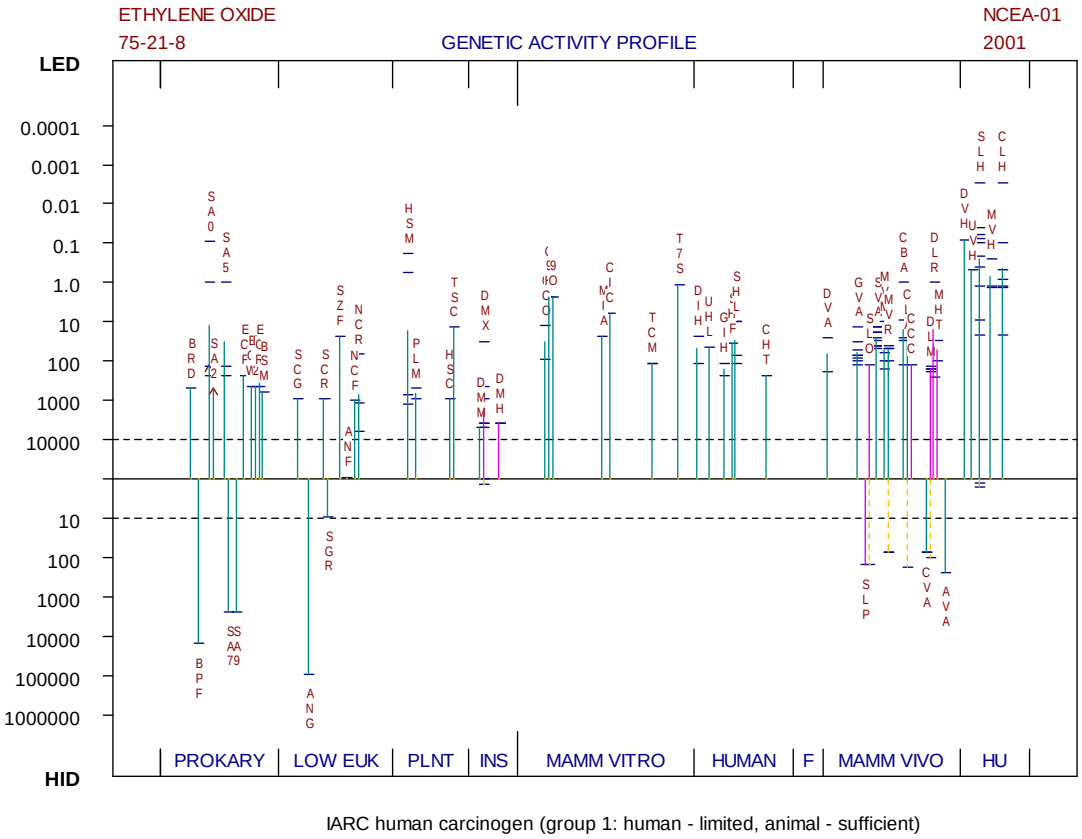

Figure 3. Display of 203 data sets, including bacteria, fungi, plants, insects, and mammals (in vitro and in vivo), measuring the full range of genotoxic endpoints. (This is an updated version of the figure in IARC, 1994.)

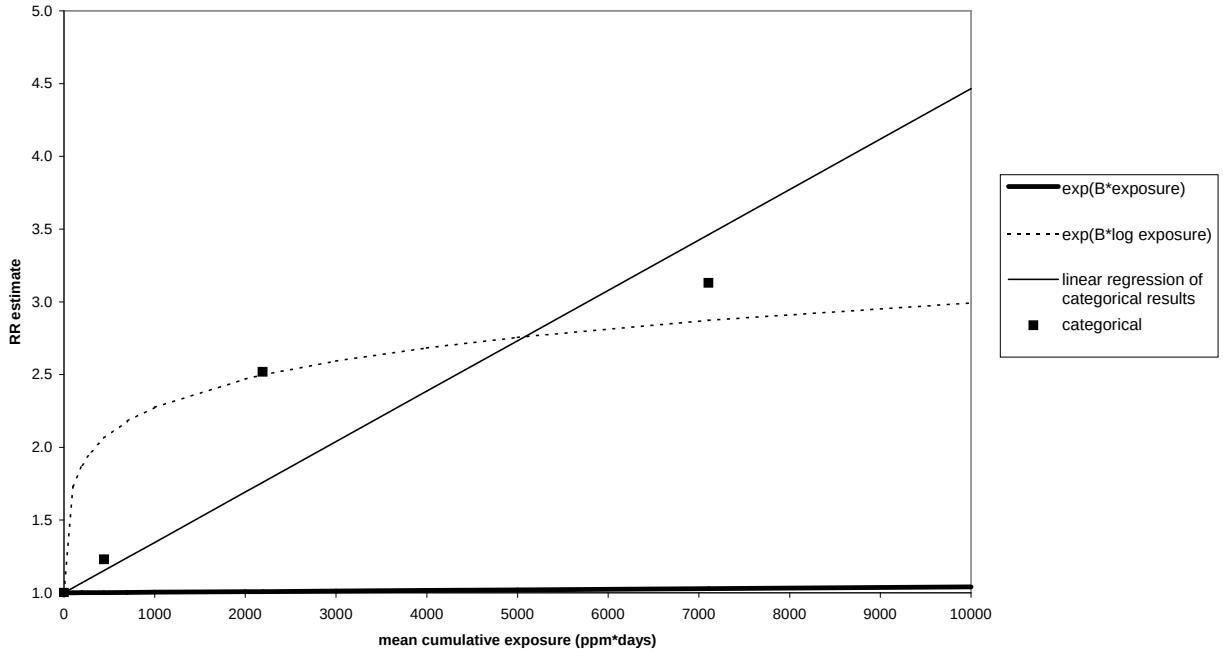

Figure 4. RR estimate for lymphohematopoietic cancer in males vs. mean exposure (from Steenland et al., 2004, Table 6, Cox regression results, except for linear regression [see text]; log and categorical exposures with 15-year lag), unadjusted for continuous exposure. (Highest categorical exposure quartile not shown.)

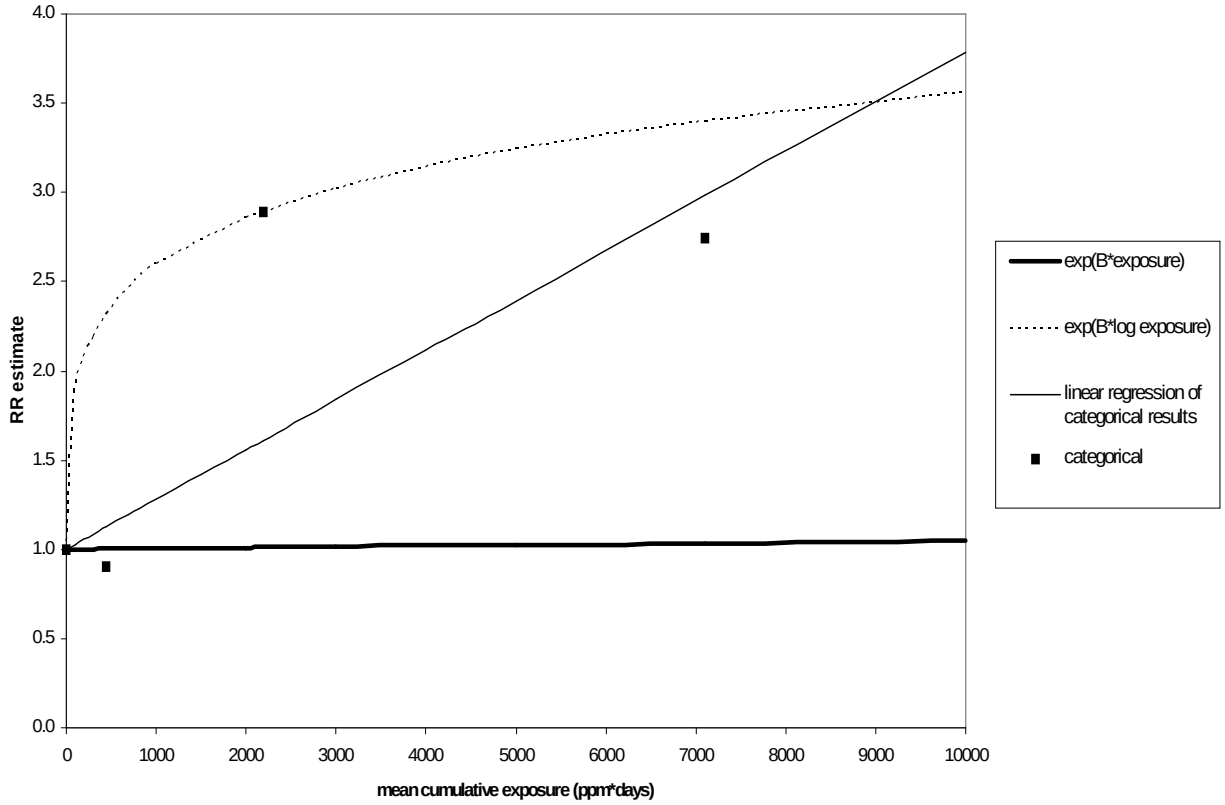

Figure 5. RR estimate for "lymphoid" cancer in males vs. mean exposure (from Steenland et al., 2004, Table 7, Cox regression results, except for linear regression [see text]; log and categorical exposures with 15-year lag), unadjusted for continuous exposure. (Highest categorical exposure quartile not shown.)

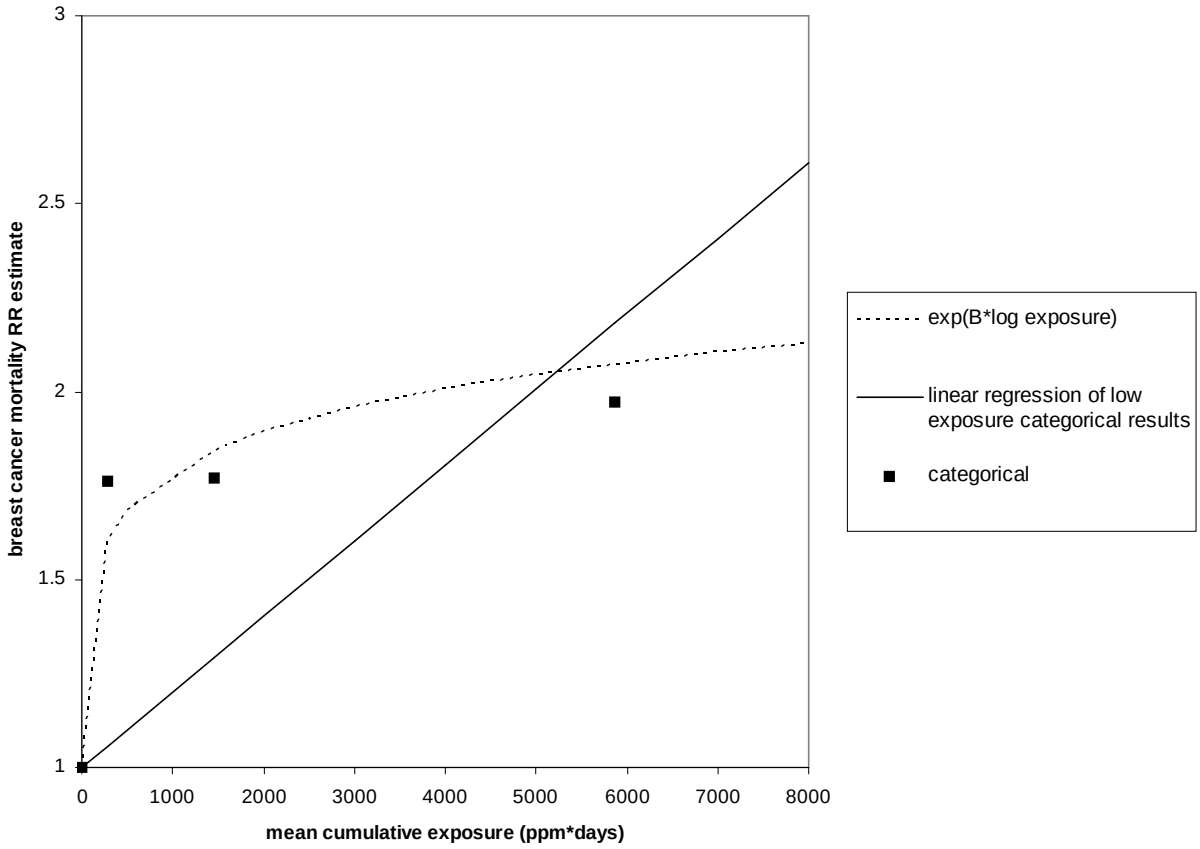

Figure 6. RR estimate for breast cancer mortality in females vs. mean exposure (from Steenland et al., 2004, Table 8, Cox regression results, except for linear regression [see text]; with 20-year lag), unadjusted for continuous exposure. (Highest categorical exposure quartile not shown.)

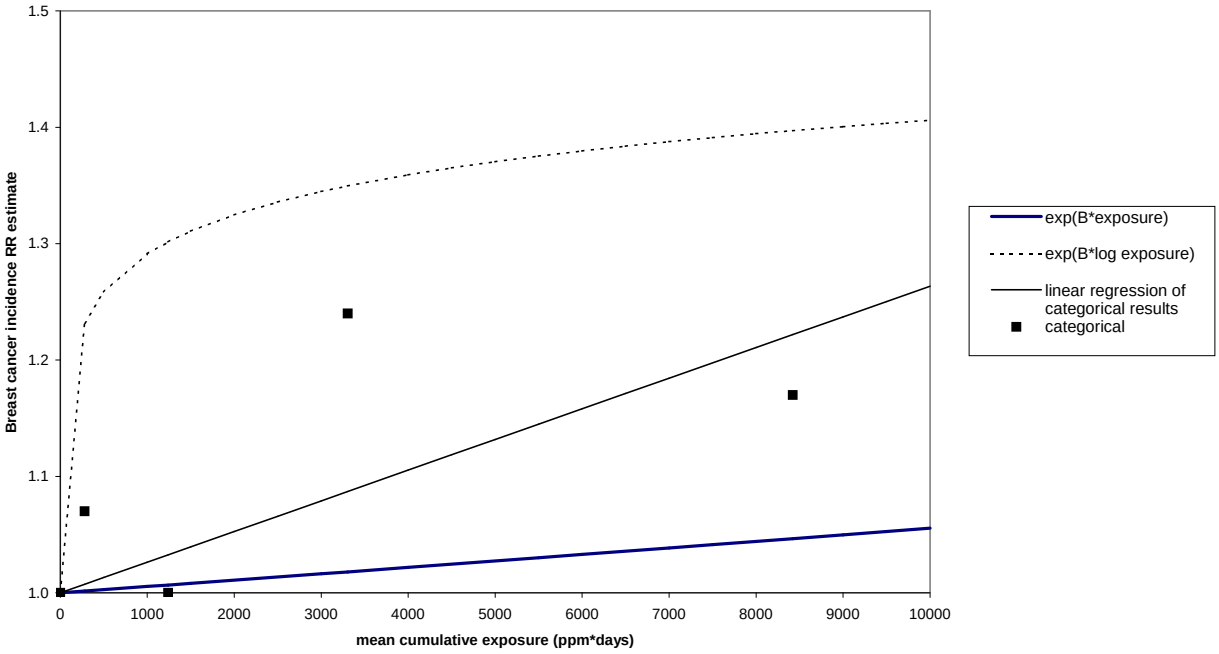

Figure 7. RR for breast cancer incidence in females (full cohort) vs. mean exposure (from Steenland et al., 2003, Table 4, Cox regression results, except for linear regression [see text]; 15-year lag), unadjusted for continuous exposure. (Highest categorical exposure quintile not shown.)

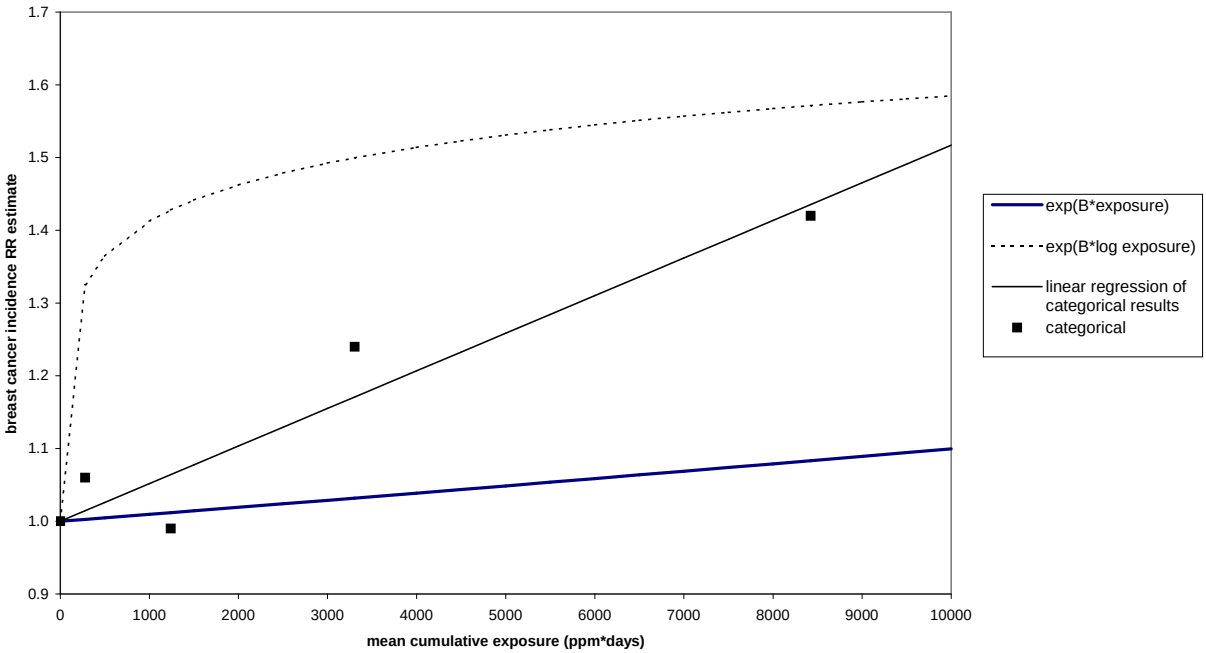

Figure 8. RR for breast cancer incidence in females (subcohort with interviews) vs. mean exposure (from Steenland et al., 2003, Table 5, Cox regression results, except for linear regression [see text]; 15-year lag), unadjusted for continuous exposure. (Highest categorical exposure quintile not shown.)

APPENDIX A: CRITICAL REVIEW OF EPIDEMIOLOGIC EVIDENCE

A.1. EARLY EVALUATIONS

In 1985, the U.S. Environmental Protection Agency (EPA) published a health assessment of the potential carcinogenicity of ethylene oxide (EtO) (U.S. EPA, 1985). The report concluded that exposure to this chemical was "probably carcinogenic to humans," and it was classified as Group B1 according to *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 1986). The epidemiological evidence was considered to be "limited," bordering on "inadequate." Evidence from three studies of two cohorts (Hogstedt et al., 1979a, b, 1984), in which the risk of leukemia was reported to be statistically significant, provided the basis for this determination. A fourth study by Morgan et al. (1981) reported an increased mortality from pancreatic cancer and Hodgkin's disease that was statistically significant ($p<0.05$). Critical reviews of these studies are found in the 1985 health assessment document and are not reviewed in the current document. Studies published since 1985 are reviewed in this Appendix.

A.2. BACKGROUND

On the basis of studies indicating that EtO was a strong mutagen and that exposure to EtO produced increased chromosomal aberrations in human lymphocytes (Rapoport, 1948; Ehrenberg and Gustafsson, 1959; Ehrenberg and Hallstrom, 1967), Hogstedt and colleagues studied three small, independent cohorts of workers from Sweden. Reports on two of these cohorts (Hogstedt et al., 1979a, b, 1984) were reviewed in the earlier health assessment document (U.S. EPA, 1985). These two small cohorts plus a third group of EtO-exposed workers from a third independent plant in Sweden were then combined and studied as one cohort (Hogstedt et al., 1986; Hogstedt, 1988). A review of this reconstituted cohort study and subsequent independent studies is presented in Section A3.

Shortly after the third Hogstedt study was completed, another independent study of EtO-exposed employees was completed (Gardner et al., 1989) on a cohort of workers from four companies and eight hospitals in Great Britain, and it was followed by a third independent study on a cohort of exposed workers in eight chemical plants from the Federal Republic of Germany (Kiesselbach et al., 1990). A followup study of the Gardner et al. (1989) cohort was recently conducted by Coggon et al. (2004).

Greenberg et al. (1990) was the first in a series of studies of workers exposed to EtO at two production facilities in the Kanawha Valley (South Charleston, WV). The workers at these two facilities were studied later by Teta et al. (1993, 1999) and Benson and Teta (1993) and

became the basis for several important quantitative risk assessment analyses (Teta et al., 1999; EOIC, 2001).

Another independent study of EtO-exposed workers in 14 sterilizing plants from across the United States was completed by the National Institute for Occupational Safety and Health (Steenland et al., 1991; Stayner et al., 1993). The Stayner et al. (1993) paper presents the exposure-response analysis performed by the NIOSH investigators. These same workers were studied again from a different perspective by Wong and Trent (1993). The NIOSH investigators recently completed a followup of the mortality study (Steenland et al., 2004) and a breast cancer incidence study based in the same cohort (Steenland et al., 2003). The results of the Steenland et al. (2003, 2004) analyses are the basis for the quantitative assessment in this document, for reasons explained in the review and summary sections of this Appendix.

Several additional studies of lesser importance have been done on EtO-exposed cohorts of workers in Sweden (Hagmar et al., 1991, 1995), Italy (Bisanti et al., 1993), Belgium (Swaen et al., 1996), and western New York State (Norman et al., 1995), and other parts of the United States (Olsen et al., 1997). These studies are discussed in the following review, but they provide limited information to the overall discussion of whether EtO induces cancer in humans.

The more important studies, which are discussed in detail in the summary, are those at two facilities in the Kanawha Valley in West Virginia (Greenberg et al., 1990; Benson and Teta, 1993; Teta et al., 1993, 1999) and at 14 sterilizing plants around the country (Stayner et al., 1993; Steenland et al., 1991, 2003, 2004). These studies indicate that a great deal of effort and care was expended to ensure that they were done well. They have sufficient followup to analyze latent effects, attempts were made to develop dose-response relationships using reasonable assumptions about early exposures to EtO, and the cohorts appear to be large enough to test for small differences.

A.3. INDIVIDUAL STUDIES

A.3.1. HOGSTEDT ET AL. (1986), HOGSTEDT (1988)

Hogstedt et al. (1986) combined workers from several cohorts for a total of 733 workers, including 378 workers from two separate and independent occupational cohort mortality studies by Hogstedt et al. (1979a, b) and 355 employees from a third EtO production plant who had not been previously examined. The combined cohort was followed until the end of 1982. The first cohort comprised employees from a small technical factory in Sweden where hospital equipment was sterilized with EtO. The second was from a production facility where EtO was produced by the chlorohydrin method from 1940 to 1963. The third was from a production facility where EtO was made by the direct oxidation method from 1963 to 1982.

In the update of the 1986 occupational mortality report (Hogstedt, 1988), the cohort inexplicably was reduced to 709 employees (539 men; 170 women). Followup for mortality was extended to the end of 1985. The author reported that 33 deaths from cancer had occurred, whereas only 20 were expected in the combined cohort. The excesses that are significant are due mainly to an increased risk of stomach cancer at one plant and an excess of blood and lymphatic malignancies at all three. Seven deaths from leukemia occurred, whereas only 0.8 were expected (standard mortality ratio [SMR] = 9.2). Ten deaths due to stomach cancer occurred versus only 1.8 expected (SMR = 5.46). The results tend to agree with those from clastogenic and short-term tests on EtO (Ehrenberg and Gustafsson, 1959). The authors believe that the large number of positive cytogenetic studies demonstrating increased numbers of chromosomal aberrations and sister chromatid exchanges at low-level exposure to EtO indicate that the lymphatic and hematopoietic systems are particularly sensitive to the genotoxic effects of EtO. They concluded that the induction of malignancies even at low-level and intermittent exposures to EtO should be "seriously considered by industry and regulating authorities."

The average air EtO concentrations in the three plants were as follows: In Plant 1 (Hogstedt et al., 1979b) in 1977, levels ranged from 2 to 70 ppm in the storage hall. The average 8-hour time-weighted average (TWA) concentration in the breathing zone of the employees was calculated as 20 ppm +/- 10 ppm. Measured concentrations were 150 ppm on the floor outside of the sterilized boxes and 1,500 ppm inside.

In Plant 2 (Hogstedt et al., 1979a), EtO was produced through the chlorohydrin process. Between 1941 and 1947, levels probably averaged about 14 ppm, with occasional exposures up to 715 ppm. Between 1948 and 1963, levels were in the range of 6 ppm to 28 ppm. After 1963, when production of EtO came to an end, levels ranged from less than 1 ppm to as much as 6 ppm.

In Plant 3 (Hogstedt et al., 1986), the 355 employees were divided into subgroups. Subgroup A had almost pure exposure to EtO. Subgroup B had principal exposure to EtO but also exposure to propylene oxide, amines, sodium nitrate, formaldehyde, and 1,2-butene oxide. Workers in the remaining subgroup C were maintenance and technical service personnel, who had multiple exposures, including EtO. Concentration levels in Plant 3 are shown in Table A-1.

In the earlier studies (Hogstedt et al., 1979a, b) of two of the plants that contributed workers to this cohort, the authors allude to the fact that there was exposure to benzene, ethylene dichloride, ethylene chlorohydrin, ethylene, and small amounts of bis-(2-chloroethyl) ether, as well as other chemicals in the respective plants. Although 170 women were present in the workforce, no gender differences in risk were analyzed separately by the investigators. Of 16 patients with tumors in the two exposed cohorts, there were three cases of leukemia (0.2 expected), six cases of alimentary tract cancer, and four cases of urogenital cancer. Of the 11

Table A-1. Estimated 8-hour time-weighted average ethylene oxide exposure, Plant 3

Group	1963–1976	1977–1982
A (n = 128)	5–8 ppm	1–2 ppm
B (n = 69)	3 ppm	1 ppm
C (n = 158)	1–3 ppm	0.4–1.6 ppm

Source: Hogstedt et al., 1986

cancer cases in the full-time exposed cohort, 5.9 were expected ($p<0.05$). This study was criticized by Divine and Amanollahi (1986) for several reasons. First, they believed that the study's strongest evidence in support of a carcinogenic claim for EtO was only a "single case of leukemia" in subgroup C of Plant 3, where the workers had multiple chemical exposures; however, there were no cases in subgroups A or B of Plant 3. Hogstedt et al. (1986) countered that the expectation of leukemia in these two subgroups were 0.04 and 0.02, respectively, and that the appearance of a case could only happen if EtO had "outstanding carcinogenic properties at low levels." Divine and Amanollahi also pointed out that a study (Morgan et al., 1981) of a cohort similar to that of Plant 3 found no leukemia cases or evidence of excessive mortality. Hogstedt et al. replied that Morgan et al. stated in their paper that the statistical power of their study to detect an increased risk of leukemia was not strong.

Divine and Amanollahi (1986) also stated that the exposures to EtO were considerably higher in plants 1 and 2 than in Plant 3; therefore, combinations would "normally preclude comparisons between the plants for similar causes of adverse health." This potential problem could be resolved by structuring exposure gradients to analyze risk. Furthermore, they noted, Plant 1 was a nonproduction facility involved in sterilization of equipment. Plant 2 used the chlorohydrin process for making EtO, and Plant 3 used the direct oxygenation process. Although these conditions are obviously different, they "are grouped together as analogous." This criticism would, in most instances, be valid only because the methods for producing EtO differ and there were differing exposures to multiple chemicals.

However, these concerns are not supported by the evidence. In all three plants the leukemia risk was elevated, even if only slightly in Plant 3. This suggests that there may have been a common exposure, possibly to EtO, endemic to all three plants that was responsible for the measured excesses. Noteworthy is the elevated risk of leukemia seen in Plant 1 (3 observed vs. 0.14 expected), where the exposures were almost exclusively to EtO in the sterilization of equipment. The argument that Plant 1 leukemias form a "chance cluster," as Shore et al. (1993)

claim, and as such should be excluded from any analysis does not preclude the possibility that these cases are in reality the result of exposure to EtO. Hogstedt argues that earlier remarks by Ehrenberg and Gustafsson (1959) that EtO "constituted a potential cancer hazard" on the basis of a considerable amount of evidence other than epidemiologic should have served as a warning that the increased risk seen in Plant 1 was not necessarily a "chance cluster," and because the chlorohydrin process was not in use in Plant 1, it cannot be due to exposure to a chemical in the chlorohydrin process.

A.3.2. GARDNER ET AL. (1989)

Gardner et al. (1989) completed a cohort study of 2,876 men and women who had potential exposure to EtO. The cohort was identified from employment records at four companies that had produced or used EtO since the 1950s and from eight hospitals that have had EtO clinical sterilizing units since the 1960s, and it was followed to December 31, 1987. All but 1 of the 1,012 women and 394 of the men in the cohort worked at one of the hospitals. The remaining woman and 1,470 men made up the portion of the cohort from the four companies. By the end of the followup, 226 members (8% of the total cohort) had died versus 258.8 expected. Eighty-five cancer deaths were observed versus 76.64 expected.

No clear excess risk of leukemia (3 observed vs. 2.09 expected), stomach cancer (5 observed vs. 5.95 expected), or breast cancer (4 observed vs. 5.91 expected) was present as of the cut-off date. "Slight excesses" of deaths due to esophageal cancer (5 observed vs. 2.2 expected), lung cancer (29 observed vs. 24.55 expected), bladder cancer (4 observed vs. 2.04 expected), and NHL (4 observed vs. 1.63 expected) were noted, although an adjustment made to reflect local "variations in mortality" reduced the overall cancer excess from 8 to only 3. According to the authors' published tabulations, all three leukemias identified in this study fell into the longest latent category (20 years or longer), where only 0.35 were expected. All three were in the chemical plants. This finding initially would seem to be consistent with experimental animal evidence demonstrating excess risks of hematopoietic cancer in animals exposed to EtO. But the authors note that since other known leukemogens were present in the workplace, the excess could have been due to a confounding effect.

The hospitals began using EtO during or after 1962, whereas all of the chemical companies had handled EtO from or before 1960. In the hospitals there was occasional exposure to formaldehyde and carbon tetrachloride but few other confounding agents. On the other hand, the chemical workers were exposed to a wide range of compounds including chlorohydrin, propylene oxide, styrene, and benzene. The earliest industrial hygiene surveys in 1977 indicated that the TWA average exposures were less than 5 ppm in almost all jobs and less than 1 ppm in many. No industrial hygiene data were available for any of the facilities prior to 1977, although it

is stated that peaks of exposure up to several hundred ppm occurred as a result of operating difficulties in the chemical plants and during loading and unloading of sterilizers in the hospitals. An odor threshold of 700 ppm was reported by both manufacturers and hospitals, according to the authors. The authors assumed that past exposures were somewhat higher without knowing precisely what they were. An attempt was made to classify exposures into a finite number of subjectively derived categories (definite, possible, continual, intermittent, and unknown). This exercise produced no discernable trends in risk of exposure to EtO. However, the exposure status classification scheme was so vague as to be useless for determining risk by gradient of exposure to EtO.

It is of interest that all three of the leukemia deaths entailed exposure to EtO, with very little or no exposure to benzene, according to the authors. The findings are not inconsistent with those of Hogstedt et al. (1986) and Hogstedt (1988). The possibility of a confounding effect other than benzene in these chemical workers cannot entirely be ruled out. Other cancers were slightly in excess, but overall there was little increased mortality from cancer in this cohort. It is possible that if very low levels of exposure to EtO had prevailed throughout the history of these hospitals and plants, the periods of observation necessary to observe an effect may not have been long enough.

A followup study of this cohort conducted by Coggon et al. (2004) is discussed below.

A.3.3. KIESSELBACH ET AL. (1990)

Kiesselbach et al. (1990) carried out an occupational cohort mortality study of 2,658 men from eight chemical plants in the Federal Republic of Germany (FRG) that were involved in the production of EtO. The method of production is not stated. At least some of the plants that were part of an earlier study by Thiess et al. (1982) were included. Each subject had to have been exposed to EtO for at least 1 year sometime between 1928 and 1981 before person-years at risk could start to accumulate. Most exposures occurred after 1950. By December 31, 1982, the closing date of the study, 268 men had died (about 10% of the total cohort), 68 from malignant neoplasms. The overall SMR for all causes was 0.87, and for total cancer the SMR was 0.97, based on FRG rates. The authors reported that this deficit in total mortality indicates a healthy-worker effect.

The only remarkable findings here are slightly increased risks of death from stomach cancer (14 observed vs. 10.15 expected, SMR = 1.4), cancer of the esophagus (3 observed vs. 1.5 expected, SMR = 2), and cancer of the lung (23 observed vs. 19.86 expected, SMR = 1.2). Although the authors claimed that they looked at latency, only stomach cancer and total mortality has a latency analysis included. This was accomplished by not counting the first 10 years of followup in the parameter “years since first exposure.” This study is limited by the lack of further

latency analyses at other cancer sites. The risk of stomach cancer shows only a slight nonsignificant trend upward with increasing latency. Only two leukemias were recorded versus 2.35 expected.

This is a largely unremarkable study, with few findings of any significance. No actual exposure estimates are available. The categories of exposure that the authors constructed are "weak," "medium," and "strong." It is not known whether any of these categories is based on actual measurements. No explanation of how they were derived is provided except that the authors claim that the information is available on 67.2% of the members of the cohort. If the information was based on job categories, it should be kept in mind that exposures in jobs that were classified the same from one plant to the next may have produced entirely different exposures to EtO. The tabular data regarding these exposure categories shows that only 2.4% of all members of the cohort were considered "strongly" exposed to EtO. Although 71.6% were classified as "weak," the remaining 26% were considered as having "medium" exposure to EtO.

This is largely a study in progress, and further followup will be needed before any definite trends or conclusions can be drawn. The authors reported that only a median 15.5 years of followup had passed by the end of the cutoff date, whereas the median length of exposure was 9.6 years. Before any conclusions can be made from this study several additional years of followup would be needed with better characterization of exposure.

A.3.4. GREENBERG ET AL. (1990)

Greenberg et al. (1990) retrospectively studied the mortality experience of 2,174 men employed in a Union Carbide Corporation (UCC) chemical plant in West Virginia that used or produced EtO. The referent comparison population was general U.S. population death rates. Regional population death rates were found to be similar to those of the U.S. general population. Followup began either on January 1, 1940, if exposure to EtO began sooner, or on the date when exposure began if it occurred after January 1, 1940. Followup ended on December 31, 1978. Total deaths equaled 297 versus 375.9 expected (SMR = 0.79). Only 60 total cancer deaths were observed versus 74.6 expected (SMR = 0.81). These deficits in mortality are a manifestation of the healthy-worker effect. In spite of this, nonsignificant elevated risks of cancer of the liver, unspecified and primary, (3 observed vs. 1.8 expected, SMR = 1.67), pancreas (7 observed vs. 4.1 expected, SMR = 1.7), and leukemia and aleukemia (7 observed vs. 3 expected, SMR = 2.33) were noted.

The authors also reported that in 1976, 3 years prior to the end of followup, an industrial hygiene survey found that airborne levels of EtO were low, less than 1 ppm 8-hour TWA. In maintenance workers, levels averaged between 1 and 5 ppm 8-hour TWA. These measurements were the first large-scale monitoring of respirable EtO at this company, and the results indicated

that some exposure levels were as high as 66 ppm 8-hour TWA. Because of the lack of information about exposures before 1976, the authors developed a prior exposure scheme on the basis of the 1976 survey and the potential for exposure by each department on the basis of occurrence of dermatological or other medical problems. This scheme envisioned designating every department according to one of three categories of exposure to EtO: low, intermediate, or high.

Except for two cases of leukemia, all the victims of pancreatic cancer and leukemia began their work—and hence exposure to EtO—many years prior to their deaths. Four of the seven leukemia victims had been assigned to the chlorohydrin department; only 0.8 deaths (SMR = 5) would have been expected in this department of only 278 workers. Six pancreatic cancer victims were assigned to the chlorohydrin department, whereas only 0.98 deaths would have been expected to occur (SMR = 6.12).

All seven leukemia victims, including the four in the chlorohydrin department, were listed by the authors as having only low exposure to EtO. In contrast, in the department where exposure to EtO was probably the highest, no leukemia deaths and only one pancreatic cancer death occurred. However, according to the authors, exposures to EtO in the EtO direct oxidation production department at a similar plant in Texas (discussed in Joyner, 1964) were "probably in the range of 10–20 ppm" and when the chlorohydrin process was used, the "levels of exposure to EtO were probably somewhat higher" (in the West Virginia Kanawha Valley plants) because "technology, construction materials and work practices were from an earlier time" and there was also "no control room and production equipment was indoors." These observations would seem to argue against the assumption that the four victims who were assigned to the chlorohydrin department would fall into a low exposure category, based on estimated levels of exposure in a similar operation at the Texas plant.

The authors hypothesized that leukemia and pancreatic cancers have been associated with production of ethylene chlorohydrin or propylene chlorohydrin or both in the chlorohydrin department. This reasoning is premised upon their exposure category construct, which places most of the leukemia and pancreatic cancer victims in that department. Because the exposure classification was not based on any actual individual TWA measurements prior to 1976 but only on the potential for exposure, it is speculative to assume accuracy in the designation of individuals to such categories.

If the exposure scheme is not considered—because it appears to be somewhat subjective—a borderline significant excess risk of leukemia occurred in a group of workers alleged to have had some exposure to EtO. The question is whether the slightly increased risk of leukemia and pancreatic cancer was a consequence of exposure to EtO or to other chemicals such

as ethylene dichloride, propylene chlorohydrin, bis-chloroethyl, and dichloroethane in the chlorohydrin manufacturing process. This study does not resolve the issue.

A.3.5. STEENLAND ET AL. (1991)

In an industrywide analysis by the National Institute for Occupational Safety and Health, Steenland et al. (1991) studied EtO exposure in 18,254 workers (55% female) identified from personnel files of 14 plants that had used EtO for sterilization of medical equipment, treating spices, or testing sterilizers. Each of the 14 plants (from 75 facilities surveyed) that were considered eligible for inclusion in the study had at least 400 person-years at risk prior to 1978. Within each eligible facility, at least 3 months of exposure to EtO qualified an employee for inclusion in the cohort. Employees, including all salaried workers, who were "judged never to have been exposed to EtO" on the basis of industrial hygiene surveys were excluded. Followup ended December 31, 1987. The cohort averaged 16 years of latency. Approximately 86% achieved the 9-year latent point, but only 8% reached the 20-year latency category. The average year of first exposure was 1970, and the average length of exposure was 4.9 years. The workers' average age at entry was not provided, nor was an age breakdown. Nearly 55% of the cohort were women.

Some 1,137 workers (6.4%) were found to be deceased at the end of the study period, upon which the underlying cause of death was determined for all but 450. If a member was determined to be alive as of January 1, 1979, but not after and no death record was found in the National Death Index through December 31, 1987, then that member was assumed to be alive for the purposes of the life-table analysis and person-years were accumulated until the cut-off date. Altogether, 4.5% of the cohort fell into this category. This procedure would tend to increase the expected deaths and, as a consequence, potentially bias the risk ratio downward if a sizable number of deaths to such persons during this period remained undiscovered to the researchers.

In the total cohort no significantly increased risks of death from any site-specific cancer were noted. Analyses by job categories and by duration of exposure indicated no excess risks of cancer when compared with the rate in the general population. However, there was an increased trend in the risk of hematopoietic cancers, all sites, with increasing lengths of time since first exposure. After 20 years latency, the SMR was 1.76, based on 13 cases. The test for trend was significant at $p=0.03$. For men (45%), without regard for latency, the SMR for hematopoietic cancer was a significant 1.55 ($p<0.05$), based on 27 cases. Among men with long latency (greater than 20 years) and the longest duration of exposure (greater than 7 years) the SMR for hematopoietic cancers was 2.63, based on 7 deaths ($p<0.05$).

The authors pointed out that the SMR for leukemia among men was 3.45, based on 5 deaths ($p<0.05$), for deaths in the latter period of 1985 to 1987. For kidney cancer, the SMR was

3.27, based on 6 deaths ($p<0.05$), after 20 years latency. The authors also reported on a significant excess risk ($p<0.05$) of lymphosarcoma-reticulosarcoma in men (SMR = 2.6), based on 7 deaths. Women had a lower nonsignificant rate. The risk of breast cancer was also nonsignificant (SMR = 0.85 based on 42 cases). The authors hypothesized that men were more heavily exposed to EtO than were women because "men have historically predominated in jobs with higher levels of exposure." However, the lack of an association between EtO exposure and lymphohematopoietic cancer in females was also observed in the exposure-response analyses of this cohort, including in the highest exposure category, performed by Stayner et al. (1993) and discussed below.

Industrial hygiene surveys indicated that sterilizer operators were exposed to an average personal 8-hour TWA EtO level of 4.3 ppm, whereas all other workers averaged only 2 ppm, based on 8-hour samples during the period 1976 to 1985. These latter employees primarily worked in production and maintenance, in the warehouse, and in the laboratory. This was during a time when engineering controls were being installed to reduce worker's exposure to EtO; earlier exposures may have been somewhat higher. The authors reported that no evidence of confounding exposure to other occupational carcinogens was documented.

The authors concluded that there was a trend toward an increased risk of death from hematopoietic cancer with increasing lengths of time since the first exposure to EtO. This trend might have been enhanced if the authors had added additional potential deaths identified from the 820 (4.5%) "untraceable" members of the cohort from 1979 to 1987. The authors felt that their results were not conclusive for the relatively rare cancers of a priori interest, based on the limited number of cases and the short followup. The cohort averaged 16 years of latency and 86% had at least 9 years but only 8% reached the 20-year latent category.

Exposure-response analyses were conducted by Stayner et al. (1993) and are discussed below. More recently, a followup mortality study (Steenland et al., 2004) and a breast cancer incidence study (Steenland et al., 2003) of this cohort were conducted; these are also discussed below.

A.3.6. TETA ET AL. (1993)

In a reanalysis of the cohort of 2,174 male UCC workers studied by Greenberg et al. (1990), Teta and her colleagues excluded the 278 workers in the chlorohydrin unit in which Greenberg and colleagues found a high risk of leukemia and pancreatic cancer, thereby removing the potential confounding of the chlorohydrin process. The 1,896 men remaining in the cohort were followed for another 10 years, through all of 1988. It was determined from the Greenberg et al. study that there were no elevated cancer risks in these remaining workers up to December 31, 1978; therefore it was not likely that any significant "risks" would be found without extending the period of followup.

Teta et al. (1993) reported that the average duration of exposure was more than 5 years and the average followup was 27 years. The reanalysis demonstrated no increased risk of overall cancer, nor of leukemia, NHL or brain, pancreatic, or stomach cancer. The SMR for total deaths, based on comparison with mortality from the general population, was 0.8 (observed = 431). The SMR for total cancer was 0.9 (observed = 110). No site-specific cancers were significantly elevated. Although the authors concluded that this study did not indicate any significant trends of site-specific cancer with increasing duration of potential exposure to EtO, there appeared to be a nonsignificant increasing trend of leukemia and aleukemia as well as stomach cancer with increasing duration of potential exposure (Table A-2).

Table A-2. Relative risk (RR) estimates and observed deaths (obs) for selected causes by cumulative duration of assignments in departments in years using or producing ethylene oxide

Cause of death	Never assigned RR (obs)	Less than 2 yrs RR (obs)	2 to 9 years RR (obs)	10 or more years RR (obs)
Stomach cancer	1(79)	0.64 (1)	2.77 (5)	2.62 (2)
Leukemia and aleukemia	1(75)	0 (0)	1.11 (2)	2.54 (3)

Source: Adapted from Teta et al., 1993

The average EtO levels reported by Greenberg et al. (1990) were less than 1 ppm in all areas of the plant, based on the 1976 monitoring. Teta et al. estimated that in the 1960s, exposure in the units producing EtO by direct oxidation ranged from 3 to 20 ppm 8-hour TWA, with operator concentration estimated at between 5 and 10 ppm 8-hour TWA. These estimates were based on an industrial hygiene survey conducted at another company facility in Texas that used the same process as the two plants in West Virginia from which the Greenberg et al. cohort was taken. Ethylene oxide was produced via the chlorohydrin process in a closed building during these early years (1925 to 1957). Levels of exposure to EtO would have been higher than in the direct oxidation production process because of start-up difficulties, fewer engineering controls, less complex equipment, and the enclosed building. Nausea, dizziness, and vomiting were documented in the employees who made numerous visits to the medical department in 1949. These acute effects occur in humans at exposures of several hundred ppm, according to the authors.

During the time periods under investigation, the estimated exposure ranges were >14 ppm from 1925 to 1939; 11–14 ppm from 1940 to 1956; 5–10 ppm from 1957 to 1973 ; and <1 ppm from 1974 to 1988, with frequent peaks of several hundred ppm in the earliest period and some peaks of similar intensity in the 1940s to mid-1950s. In the absence of monitoring data prior to 1976, these estimates cannot be confirmed. Furthermore, workers were eliminated from the analysis if they had worked in the chlorohydrin unit because of the assumption that the increased risks of leukemia and pancreatic cancer were possibly due to exposure to something in the chlorohydrin process, as conjectured by Greenberg et al. (1990). It is still possible that exposure to EtO in workers in this process might have produced the increased risks of leukemia seen in the total cohort; however, even when the confounding influence of the chlorohydrin process is removed there still remains the suggestion of a trend of an increasing risk of leukemia and aleukemia with increasing duration of exposure to EtO in the remaining cohort members, based on the numbers shown in Table A-2.

The authors indicated that their findings do not confirm the findings in experimental animal studies and are not consistent with the earliest results reported among EtO workers. They also noted that they did not observe any significant trend of increasing risks of stomach cancer (n = 8) or pancreatic, brain, or nervous system cancer or leukemia (n = 5) with increasing duration of exposure. No latency analysis was conducted in this study.

In a later analysis, Teta et al. (1999) updated their 1993 study of UCC workers and fitted dose-response models to the revised UCC data and to the NIOSH data (Steenland et al., 1991). They reported that latency and lagging of dose did not appreciably affect the fitted Poisson regression models to these data, which they concluded were the best studies for evaluating dose-response relationships. Because Teta et al. (1999) did not present aggregate risk ratios in the categories used to model dose-response relationships, the only comparison that could be made between the UCC and NIOSH data is based on the fitted models. These models are almost identical for leukemia, but for the lymphoid category, the risk according to the fitted model for the UCC data decreased as a function of dose, whereas the risk for the modeled NIOSH data increased as a function of dose. It is possible that the difference is due to regional practices in coding death certificates for specific types of leukemia.

A.3.7. BENSON AND TETA (1993)

In a companion mortality study (Benson and Teta, 1993), the remaining 278 employees who were identified by Greenberg et al. (1990) as having worked at some time in the chlorohydrin process and who were not included in the cohort of Teta et al. (1993) were followed to the end of 1988. Altogether, 40 cancer deaths occurred versus 30.8 expected (SMR = 1.3) in the subcohort of chlorohydrin workers. In Greenberg et al., significant elevated risks of pancreatic cancer and

leukemia and aleukemia occurred in only those workers assigned to the chlorohydrin process. Benson and Teta noted a significantly increased risk of pancreatic cancer (SMR = 5, 8 observed deaths, $p<0.05$) in the same group and a significantly increased risk of cancer in the enlarged category of hematopoietic cancer (SMR = 3, 8 observed deaths, $p<0.05$), which included leukemia and aleukemia, after an additional 10 years of followup.

The authors concluded that these cancers were likely work-related and some exposure in the chlorohydrin process, possibly to the chemical ethylene dichloride, was probably the cause. They pointed out that Greenberg et al. found that the chlorohydrin unit was likely to be a low-EtO exposure area in the West Virginia facility. The other possibility was bis-chloroethyl ether, which the authors pointed out is rated by the International Agency for Research on Cancer (IARC) as a group 3 ("not classifiable as to its carcinogenicity to humans") chemical. Circumstantial evidence seems to support the authors' contention that ethylene dichloride is the cause: IARC designated ethylene dichloride as a group 2B chemical ("possibly carcinogenic to humans"), exposure was likely heavier throughout the history of the facility, and plant medical records documented many accidental overexposures occurring to the pancreatic cancer victims prior to diagnosis. However, this conclusion is disputed by Olsen et al. (1997). Their analysis is discussed later.

A.3.8. STAYNER ET AL. (1993)

Stayner et al. (1993) provide an exposure-response analysis for the cohort study of EtO workers described by Steenland et al. (1991). Nothing was modified concerning the followup, cohort size, vital status, or cut-off date of the study. The exposure assessment and verification procedures were presented in Greife et al. (1988) and Hornung et al. (1994). Briefly, a regression model allows the estimation of exposure levels for time periods, facilities, and operations for which industrial hygiene data were unavailable. The data consisted of 2,700 individual time-weighted exposure values for workers' personal breathing zones, acquired from 18 facilities between 1976 and 1985. Arithmetic mean exposure levels by facility, year, and exposure category were calculated on the basis of grouping all sampled jobs into eight categories with similar potential for EtO exposure. The data were divided into two sets, one for developing the regression model and the second for testing it. Arithmetic means were logarithmically transformed and weighted linear regression models were fitted. Seven out of 23 independent variables tested for inclusion in the model were found to be significant predictors of EtO exposure and were included in the final model. This model predicted 85% of the variation in average EtO exposure levels.

Early historical exposures in jobs in the plants were estimated using this industrial hygiene-based regression model. In the Stayner et al. study, cumulative exposure for each worker was estimated by calculating the product of the average exposure in each job the worker held by

the time spent in that job and then summing these over all the jobs held by that worker. This value became the cumulative exposure index for that employee and reflected the working lifetime total exposure to EtO. SMRs were generated based on standard life-table analysis. The three categories of cumulative exposure were less than 1,200 ppm-days, 1,200 to 8,500 ppm-days, and greater than 8,500 ppm-days. Additionally, the Cox proportional hazards model (SAS, 1986) was used to model the exposure-response relationship between EtO and various cancer types, using cumulative exposure as a continuous variable.

Stayner and colleagues noted a marginally significant increase in the risk of hematopoietic cancers, with an increase in cumulative exposure by both the life-table analysis as well as the Cox model, although the magnitude of the increased risk was not substantial. At the highest level—greater than 8,500 ppm-days of exposure—the SMR was a nonsignificant 1.24, based on 13 cases. However, 12 of these cases were in males, whereas only 6.12 were expected. Thus, in this highest-exposure category, a statistically significant ($p<0.05$) SMR of 1.96 in males was produced. This dichotomy produced a deficit in females (1 observed vs. 4.5 expected, $p<0.05$).

The Cox analysis produced a significantly positive trend with respect to lymphoid cell tumors (combination of lymphocytic leukemia and NHL) when EtO exposures were lagged 5 years. The authors stated that these data provide some support for the hypothesis that exposure to EtO increases the risk of mortality from lymphatic and hematopoietic neoplasms. They pointed out, however, that their data do not provide evidence for a positive association between exposure to EtO and cancer of the stomach, brain, pancreas, or kidney or leukemia as a group. Breast cancer was not analyzed in this report.

This cohort was not updated with vital status information on the "untraceables" (4.5%), and cause of death information was not provided on deaths with unknown causes; thus, it lacks a complete followup and, therefore, the risk estimates may be understated. Another potential limiting factor is the information regarding industrial hygiene measurements of EtO that were completed in the plants. According to the authors, the median length of exposure to EtO of the cohort was 2.2 years and the median exposure was 3.2 ppm. It may be unreasonable to expect any findings of increased significant risks because followup was too short to allow the accumulation of mortality experience (average follow-up = 16 years; only 8% of cohort had $\geq$ 20 years follow-up).

The authors also remind us that there is a lack of evidence for an exposure-response relationship among females or for a sex-specific carcinogenic effect of EtO in either laboratory animals or humans. In fact, the mortality rate from hematopoietic cancers among the women in this cohort was lower than that of the general U.S. population. Therefore the contrast seen here is unusual.

The positive findings are somewhat affected by the presence in the cohort of one heavily exposed case (although the authors saw no reason to exclude it from the analysis), and there is a lack of definite evidence for an effect on leukemia as a group. Despite these limitations, the authors believe that their data provide support for the hypothesis that exposure to EtO increases the risk of mortality from hematopoietic neoplasms.

A.3.9. WONG AND TRENT (1993)

This study is a reanalysis of the same cohort that was studied by Steenland et al. (1990) and Stayner et al. (1993), with some differences. The cohort was incremented without explanation by 474 to a total of 18,728 employees and followed one more year, to the end of December 1988. This change in the cohort resulted in the addition of 176 observed deaths and 392.2 expected deaths. The finding of more than twice as many expected deaths as observed deaths is baffling. A reduced total mortality of this magnitude suggests that many deaths may have been overlooked. This resulted in a further reduction of the overall SMR to a significant deficit of 0.73. Sixty additional cancer deaths were added versus 65.9 expected, for an SMR = 0.9, based on 403 total cancer deaths observed versus 446.2 expected.

The authors reported no significant increase in mortality at the cancer sites found to be of most interest in previous studies, that is, stomach, leukemia, pancreas, brain and breast. They also reported the lack of a dose-response relationship and correlation with duration of employment or latency. They did report a statistically significant increased risk of NHL among men (SMR = 2.47; observed = 16, expected = 6.47; $p<0.05$) that was not dose-related and a nonsignificant deficit of NHL among women (SMR = 0.32; observed = 2, expected = 6.27). The authors concluded that the increase in men was not related to exposure to EtO but could in fact have been related to the presence of acquired immune deficiency syndrome (AIDS) in the male population. When this explanation was offered in a letter to the editor (Wong, 1991) regarding the excess of NHL reported in Steenland et al. (1991), it was dismissed by Steenland and Stayner (1993) as pure speculation. Steenland and Stayner responded that most of the NHL deaths occurred prior to the AIDS epidemic, which began in the early 1980s. They also indicated that there was no reason to suspect that these working populations would be at a higher risk for AIDS than was the general population, the comparison group.

Wong and Trent also reported a slightly increased risk of cancer in other lymphatic tissue (14 observed vs. 11.39 expected). In men, the risk was nonsignificantly higher (11 observed vs. 5.78 expected). Forty-three lymphopoietic cancers were observed versus 42 expected. In men, the risk was higher (32 observed vs. 22.22 expected). Fourteen leukemia deaths were noted versus 16.2 expected. The authors did not derive individual exposure estimates for exposure-

response analysis, such as in Stayner et al. (1993). Rather, they used duration of employment as a surrogate for exposure.

This study has many of the same limitations as the Stayner et al. (1993) study. The authors assumed that those individuals with an unknown vital status as of the cut-off date were alive for the purposes of the analysis, and they were unable to obtain cause of death information on 5% of the known deaths.

The differences between this cohort study and that of Stayner et al. (1993) are in the methods of analysis. Stayner et al. used the 9th revision of the International Classification of Diseases (ICD) to develop their site-specific cancer categories for comparison with expected cancer mortality, whereas Wong and Trent used the 8th revision. This could account for some of the differences in the observed numbers of site-specific cancers, because minor differences in the coding of underlying cause of death could lead to a shifting of some unique causes from one site-specific category to another. Furthermore, Wong and Trent did not analyze separately the category "lymphoid" neoplasms, which includes lymphocytic leukemia and NHL, whereas Stayner et al. did. Stayner et al. further developed cumulative exposure information using exposure estimates, whereas Wong and Trent used length of employment as their surrogate for exposure but did not code detailed employment histories.

Because Wong and Trent made no effort to quantify the exposures, as was the case in Stayner et al., this study is less useful in determining a exposure-response relationship. Furthermore, the assumption that a member of the cohort should be considered alive if a death indication could not be found will potentially tend to bias risk ratios downward if, in fact, a large portion of this group is deceased. In this study all untraceable persons were considered alive at the end of the followup; therefore, the impact of the additional person-years of risk cannot be gauged.

A.3.10. BISANTI ET AL. (1993)

These authors reported on a cohort mortality study of 1,971 male chemical workers licensed to handle EtO by the Italian government, whom they followed retrospectively from 1940 to 1984. Altogether, 76 deaths had occurred in this group by the end of the study period, whereas 98.8 were expected. Of those, 43 were due to cancer versus 33 expected. The cause of one death remained unknown, and 16 workers were lost to followup. A group of 637 individuals from this cohort was licensed to handle only EtO; the remaining 1,334 had licenses valid for handling other toxic gases as well. Date of licensing for handling EtO became the initiating point of exposure to EtO, although it is likely that some of these workers had been exposed previously to EtO. The regional population of Lombardia was used as the reference group from which comparison death rates were obtained.

Although there were excess risks from almost all cancers, one of the greatest SMRs was in the category known as "all hematopoietic cancers," where 6 observed deaths occurred when only 2.4 were expected (SMR = 2.5). In the subgroup "lymphosarcoma, reticulosarcoma" there were 4 observed deaths whereas only 0.6 were expected (SMR = 6.7, $p<0.05$); the remaining 2 were leukemias. The authors note that five hematopoietic cancers occurred in the subgroup of workers who were licensed to handle only EtO but no other chemicals versus only 0.7 hematopoietic cancers expected (SMR = 7.1, $p<0.05$). These deaths occurred within 10 years from date of licensing (latent period), which is consistent with the shorter latent period anticipated for this kind of cancer. According to the authors, all workers began their employment in this industry when the levels of EtO were high, although no actual measurements were available. The fact that this subgroup of workers was licensed only for handling EtO reduces the likelihood of a confounding chemical influence.

The authors concluded that the excess risk of cancer of the lymphatic and hematopoietic tissues in these particular EtO cohort members support the suggested hypothesis of a higher risk of cancer found in earlier studies, but they added that the lack of exposure information on the other industrial chemicals in the group that had a license for handling other toxic chemicals made their findings inconclusive.

This study was of a healthy young cohort, and most person-years were contributed in the latter years of observation. Many years of followup may be necessary in order to fully verify any trend of excess risks for the site-specific cancers of interest and to measure latent effects. Furthermore, the unusual deficit of total deaths versus expected contrasted with an excess of cancer deaths versus expected raises a question about the potential for selection bias when the members of this cohort were chosen for inclusion. Also, one of the study's major limitations is the lack of exposure data.

A.3.11. HAGMAR ET AL. (1991, 1995)

Cancer incidence was studied in a cohort of 2,170 EtO-exposed workers from two plants in Sweden that produced disposable medical equipment. To fit the definition for inclusion, the subjects, 1,309 women and 861 men, had to have been employed for a minimum of 12 months and some part of that employment had to have been during the period 1970–1985 in the case of one plant and 1965–1985 in the case of the other. The risk ratios were not dichotomized by gender. No records of anyone who left employment or died before January 1, 1972 in one plant and January 1, 1975 in the other were included. Expected incidence rates were generated from the Southern Swedish Regional Tumor Registries.

Because of a short followup period and the relative young age of the cohort, little morbidity had occurred by the end of the cutoff date of December 31, 1990. Altogether, 40

cancers occurred, compared with 46.3 expected. After 10 years latency, 22 cases of cancers were diagnosed versus 22.6 expected. However, 6 lymphohematopoietic tumors were observed versus 3.37 expected, and when latency is considered, this figure falls to 3 versus 1.51 expected. The authors pointed out that for leukemia the standard incidence ratio (SIR) is a nonsignificant 7.14, based on 2 cases in 930 subjects having at least 0.14 ppm-years of cumulative exposure to EtO and a minimum of 10 years latency. The authors believed that the results provided some minor evidence to support an association between exposure to EtO and an increased risk of leukemia. However, for breast cancer, no increase in the risk was apparent for the total cohort (SIR = 0.46, OBS = 5). Even in the 10 years or more latency period, the risk was less than expected (SIR = 0.36, OBS = 2).

The authors made a reasonably good attempt to determine exposure levels during the periods of employment in both plants for six job categories. Sterilizers in the years 1970–1972 were exposed to an average 40 ppm in both plants. These levels gradually dropped to 0.75 ppm by 1985–1986. Packers and developmental engineers were the next highest exposed employees, with levels in 1970–1972 of 20 to 35 ppm and by 1985–1986 of less than 0.2 ppm. During the period 1964–1966 in the older plant, EtO levels averaged 75 ppm in sterilizers and 50 ppm in packers. Peak exposures were estimated to have ranged from 500 to 1,000 ppm during the unloading of autoclaves up to 1973. The levels gradually dropped to less than 0.2 ppm in both plants by 1985–1986 in all job categories (developmental engineers, laboratory technicians, repair men, store workers, controllers, foremen, and others) except sterilizers.

These exposure estimates were verified by measurement of hydroxy ethyl adducts to N-terminal valine in hemoglobin in a sample of subjects from both plants. The adduct levels reflect the average exposure during the few months prior to the measurement of EtO. The results of this comparison were close except for sterilizers, whose air monitoring measurements were 2 to 3 times higher.

The authors pointed out two limitations in their study: a minority of subjects had a high exposure to EtO, and the median followup (11.8 years) was insufficient to assess a biologically relevant induction latency period. Although this study has good exposure information and the authors used this information to develop an exposure index per employee, they did not evaluate dose-response relationships that might have been present, nor did they follow the cohort long enough to evaluate morbidity. The strength of this study is the development of the cumulative exposure index as well as the absence of any potential confounding produced by the chlorohydrin process, which was a problem in workers who produced and manufactured EtO in other similar studies.

A.3.12. NORMAN ET AL. (1995)

These authors conducted a mortality/incidence study in a cohort of 1,132 workers, mainly women (82%), who were exposed to EtO at some time during the period July 1, 1974, through September 30, 1980. Followup was until December 31, 1987. Ethylene oxide was used at the study plant to sterilize medical equipment and supplies that were assembled and packaged there. This plant was selected for the study because in an earlier small study at this plant (Stolley et al., 1984) there was an indication that in a sample of workers the average number of sister chromatid exchanges was elevated over that of a control group selected from the nearby community. Cancer morbidity was measured by comparing cancers occurring in this cohort with those predicted from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program for the period 1981–1985 and with average annual cancer incidence rates for western New York for 1979–1984. Observed cancers were compared to expected cancers using this method.

Only 28 cancer diagnoses were reported in the cohort; 12 were for breast cancers. Breast cancer was the only cancer site in this study where the risk was significantly elevated, based on the SEER rates (SIR = 2.55, $p<0.05$). No significant excesses were seen at other cancer sites of interest: leukemia (1 observed, 0.54 expected), brain (0 observed, 0.49 expected), pancreas (2 observed, 0.51 expected) and stomach (0 observed, 0.42 expected). The authors offered no explanation except chance as to why the risk of breast cancer was elevated in these workers.

In 1980, three 2-hour samples from the plant provided 8-hour TWA exposures to sterilizer operators that ranged from 50 to 200 ppm. Corrective action reduced the levels to 5 to 20 ppm.

This study has little power to detect any significant risk of cancer at other sites because morbidity was small, chiefly as a consequence of the short followup period. The mean number of years from the beginning of followup to the end of the study was 11.4 years. In fact, the authors stated that breast cancer was the only cancer site for which there was adequate power to detect an increased relative risk. Additional weaknesses in this study include no historic exposure information and too short a period of employment in some cases (<1month) to result in breast cancer. The authors maintained that their study was inconclusive.

A.3.13. SWAEN ET AL. (1996)

A significant cluster of 10 Hodgkin's disease cases in the active white male workforce of an unidentified large chemical manufacturing plant in Belgium led to a nested case control study by Swaen et al. (1996) to determine which, if any, chemical agents within the plant may have led to the increase. By comparison with regional cancer incidence rates, the SIR for this disease was 4.97 (95% CI = 2.38–9.15) over a 23-year period, from 1966 to 1992. This suggested that an occupational exposure may have produced the significant excess risk of Hodgkin's disease seen in these workers.

The investigators randomly selected 200 individuals from a computerized sampling frame of all men ever employed at the facility. From this list of 200, workers who were actively employed at the time of diagnosis of each case were chosen as controls. No age matching was done because the authors stated that age-specific incidence rates for Hodgkin's lymphoma in the United States were relatively flat for men between ages 18 and 65. The investigators felt that a control could serve for more than one case.

Verification of the 10 cases revealed that 1 case was, in reality, a large-cell anaplastic lymphoma. Two others could not be confirmed as Hodgkin's lymphoma due to the lack of tissue. The remaining 7 were confirmed as Hodgkin's disease. In the ensuing case-control analysis, significant odds ratios (ORs) for Hodgkin's disease were observed for five chemicals, ammonia (6 cases, OR = 5.6), benzene (5 cases, OR = 11), EtO (3 cases, OR = 8.5), NaOH (5 cases, OR = 8) and oleum (3 cases, OR = 6.9), based on the number of cases and controls known to be exposed to the chemicals in question. This does not mean they were exposed only to the chemical in question.

The availability of exposure information made it possible to calculate cumulative exposure to the cases and controls of two chemicals, benzene and EtO. The cumulative exposure for benzene-exposed cases was 397.4 ppm-months versus an expected 99.7 ppm-months for the matched controls. The authors stated that one heavily exposed case was chiefly responsible for the high cumulative total for all the benzene-exposed cases; however, it was not statistically significant. Only a few studies have suggested that exposure to benzene could possibly be related to an increase in the risk of Hodgkin's disease. The cumulative total exposure to EtO for the cases was 500.2 ppm-months versus 60.2 for the matched controls, which was statistically significant, the significance being due to one extreme case.

This study is limited because the authors enumerated only cases among active employees of the workforce; therefore, the distinct possibility exists that they could have missed potential cases in the inactive workers. It is possible that latent Hodgkin's disease cases could have been identified in the controls after the controls left active employment. However, given that there were many different possible exposures to the chemicals produced in the workplaces of these employees, it is not likely that EtO or benzene could be considered solely responsible for the excess risk of Hodgkin's disease in this working group.

A.3.14. OLSEN ET AL. (1997)

Olsen et al. (1997) studied 1,361 male employees of four plants in Texas, Michigan, and Louisiana who were employed a minimum of 1 month sometime during the period 1940 through 1992 in the ethylene chlorohydrin and propylene chlorohydrin process areas. These areas were

located within the EtO and propylene oxide production plants. Some 300 deaths had occurred by December 31, 1992.

Plant A in Texas produced EtO beginning in 1941 and ceased production in 1967. Bis-chloroethyl ether, a byproduct of EtO continued to be produced at this plant until 1973. The plant was demolished in 1974. Plant B, which was nearby, manufactured EtO from 1951 to 1971 and then again from 1975 until 1980. This plant continues to produce propylene oxide. The Louisiana plant produced EtO and propylene oxide through the propylene chlorohydrin process from 1959 until 1970, when it was converted to propylene oxide production. The Michigan plant produced ethylene chlorohydrin and subsequently EtO beginning in 1936 and continuing into the 1950s. This plant produced propylene chlorohydrin and propylene oxide up to 1974.

The authors noted that exposure to EtO was likely at the plants studied in this report, but exposure was unlikely in the 278 chlorohydrin unit workers who were excluded from the cohort studied by Teta et al. (1993). Unfortunately, no actual airborne measurements were reported by Olsen et al., and thus only length of employment could be used as a surrogate for exposure.

The SMR for all causes was 0.89 (300 observed). For total cancer the SMR was 0.94 (75 observed, 79.7 expected). There were 10 lymphohematopoietic cancers versus 7.7 expected (SMR = 1.3). No significantly increased risks of any examined site-specific cancer (pancreatic, lymphopoietic, hematopoietic, and leukemia) were noted even after a 25-year induction latency period, although the SMR increased to 1.44 for lymphopoietic and hematopoietic cancer. When only the ethylene chlorohydrin process was examined after 25 years latency, the SMR increased to 1.94, based on six observed deaths. The data to support the latter observation by the authors were not presented in tabular form.

The authors concluded that there was a weak, nonsignificant, positive association with duration of employment for lymphopoietic and hematopoietic cancer with Poisson regression modeling. They stated that the results of their study provide some assurance that their cohort has not experienced a significant increased risk for pancreatic cancer and lymphopoietic and hematopoietic cancer in ethylene chlorohydrin and propylene chlorohydrin workers. They believed that this study contradicted the conclusions of Benson and Teta (1993) that ethylene dichloride, in combination with chlorinated hydrocarbons, appeared to be the causal agent in the increased risk of pancreatic cancer and hematopoietic cancer seen in their study.

Although the authors did not specifically state that ethylene dichloride was a byproduct of the chlorohydrin process in the plants they studied, the clear implication was that it must have been present. They pointed out that ethylene dichloride is readily metabolized and rapidly eliminated from the body after gavage or inhalation administration; therefore, they questioned whether experimental gavage studies (NCI, 1978) are appropriate for studying the effects of ethylene dichloride in humans. One study (Maltoni et al., 1980) found no evidence of tumor

production in rats and mice chronically exposed to ethylene dichloride vapor concentrations up to 150 ppm for 7 hours a day. Also, because this chemical is a precursor in the production of vinyl chloride monomer, the authors wondered why an increase in these two site-specific cancers had not shown up in studies of vinyl chloride workers. However, they believe that an additional 5 to 10 years of followup of this cohort would be necessary to confirm the lack of risk for the two types of cancer described above.

Another major weakness of this study is the lack of any actual airborne measurements of EtO and the chlorohydrin chemicals.

A.3.15. STEENLAND ET AL. (2004)

In an update of the earlier mortality studies of the same cohort of workers exposed to EtO described by Steenland et al. (1991) and Stayner et al. (1993), an additional 11 years of followup were added. This increased the number of deceased to 2,852. Work history data were originally gathered in the mid-1980s. Approximately 25% of the cohort continued working into the 1990s. Work histories on these individuals were extended to the last date employed. It was assumed that these employees continued in the job they last held in the 1980s. Little difference was noted when cumulative exposure was calculated with and without the extended work histories, chiefly because the exposure levels after the mid-1980s were very low. Again overall, no excess risk of hematopoietic cancer was noted based on external rates. However, as in the earlier paper, exposure-response analyses reported positive trends for hematopoietic cancers limited to males (p=0.02 for the log of cumulative exposure with a 15-year lag) using internal comparisons and Cox regression analysis. (See Table A-3 for the categorical exposure results.)

Table A-3. Cox regression results for hematopoietic cancer mortality (15-year lag) in males

Cumulative exposure (ppm-days)	Odds ratio (95% CI)
	1
>0–1,199	1.23 (0.32–4.73)
1,200–3,679	2.52 (0.69–9.22)
3,680–13,499	3.13 (0.95–10.37)
13,500+	3.42 (1.09–10.73)

The excess of these tumors was chiefly lymphoid (NHL, myeloma, lymphocytic leukemia) (see Table A-4), as in the earlier paper. A positive trend was also observed for Hodgkin's disease in males, although this was based on small numbers.

Table A-4. Cox regression results for lymphoid cell line tumors (15-year lag) in males

Cumulative exposure (ppm-days)	Odds ratio (95% CI)
0	1
>0–1,199	0.9 (0.16–5.24)
1,200–3,679	2.89 (0.65–12.86)
3,680–13,499	2.74 (0.65–11.55)
13,500+	3.76 (1.03–13.64)

The hematopoietic cancer trends were somewhat weaker in this analysis than were those reported in the earlier studies of the same cohort. This is not unexpected because most of the cohort was not exposed after the mid-1980s, and the workers who were exposed in more recent years were exposed to much lower levels because EtO levels decreased substantially in the early 1980s. No association was found in females, although average exposures were only twice as high in males (37.8 ppm-years) as in females (18.2 ppm-years), and there was enough variability in female exposure estimates to expect to be able to see a similar trend if it existed.

This study also reports a significant excess risk of breast cancer in the highest cumulative exposure quartile, with a 20-year lag (SMR = 2.07, 95% CI 1.1–3.54, n = 13) in female employees. The results using internal Cox regression analyses with a 20-year lag time produced an OR = 3.13 (95% CI 1.42–6.92) in the highest cumulative-exposure quartile. The log of cumulative exposure with a 20-year lag was found to be the best model (p=0.01) for the analyses of breast cancer. As for hematopoietic cancer in males, cumulative exposure untransformed showed a weaker trend (p=0.16). A breast cancer incidence study of this cohort is discussed in Steenland et al. (2003).

A.3.16. STEENLAND ET AL. (2003)

In a companion study on breast cancer incidence in women employees of the same cohort discussed in Steenland et al. (2004), the authors elaborated on the breast cancer findings in a subgroup of 7,576 women from the cohort (76% of the original cohort). They had to be employed

at least 1 year and exposed while employed in commercial sterilization facilities. The average length of exposure was 10.7 years. Breast cancer incidence analyses were based on 319 cases identified via interview, death certificates, and cancer registries in the full cohort, including 20 in situ carcinomas. Interviews on 5,139 women (68% of the study cohort) were obtained; 22% could not be located. Using external referent rates (SEER), the SIR was 0.87 for the entire cohort based on a 15-year lag time. When in situ cases were excluded, the overall SIR increased to 0.94. In the top quintile of cumulative exposure, with a 15-year lag time, the SIR was 1.27 (95% CI 0.94–1.69, n = 48). A significant positive linear trend of increasing risk with increasing cumulative exposure was noted (p=0.002) with a 15-year lag time. Breast cancer incidence was believed to be underascertained owing to incomplete response and a lack of coverage by regional cancer registries (68% were contacted directly and 50% worked in areas with cancer registries). An internal nested case-control analysis, which is less subject to concerns about underascertainment, produced a significant positive exposure-response with the log of cumulative exposure and a 15-year lag time (p=0.05). The top quintile was significant with an OR of 1.74 (CI 1.16–2.65) based on all 319 cases (the entire cohort).

The authors also conducted separate analyses using the subcohort with interviews, for which there was complete case ascertainment and additional information on potential confounders. In the subcohort with interview data, the odds ratio for the top quintile equaled 1.87 (CI 1.12–3.1), based on 233 cases in the 5,139 women and controlled for with respect to parity and breast cancer in a first-degree relative. Information on other risk factors was also collected—e.g., body mass index, SES, diet, age at menopause, age at menarche, breast cancer in a first-degree relative, and parity—but only parity and breast cancer in a first-degree relative were significant in the model. Continuous cumulative exposure, as well as the log cumulative exposure, lagged 15 years, produced p values for the regression coefficient of 0.02 and 0.03, respectively, for the Cox regression model, taking into account age, race, year of birth, parity, and breast cancer in a first-degree relative.

The authors concluded that their data suggest that exposure to EtO is associated with breast cancer, but because of inconsistencies in exposure-response trends and possible biases due to nonresponse and incomplete cancer ascertainment, the case for breast cancer is not conclusive. However, monotonically increasing trends in categorical exposure-response relationships are not always the norm owing to lack of precision in the estimates of exposure. Furthermore, positive trends were observed in both the full cohort and the subcohort with interviews, lessening concerns about nonresponse bias and case underascertainment.

A.3.17. KARDOS ET AL. (2003)

These authors reported on a study completed earlier by Muller and Bertok (1995) of cancer among 299 female workers who were employed from 1976 to 1993 in a pediatric ward at the county hospital in Eger, Hungary, where gas sterilizers were used. Their observation period for cancer was begun in 1987 on the assumption that cancer deaths before 1987 were not due to EtO, based on a paper by Lucas and Teta (1996). Information about the Muller and Bertok (1995) study is unavailable because the paper is in Hungarian and no translated copy is available. Kardos and his colleagues evaluated mortality among these women and found a statistically significant excess of total cancer deaths in the period from 1987 to 1999 when compared with expected deaths generated from three different comparison populations (Hungary, Heves County, and city of Eger). Altogether, 11 deaths were observed compared with, respectively, 4.38, 4.03, and 4.28 expected deaths. The SMRs are all significant at the $p < 0.01$ level. Site-specific rates were not calculated. Among the 11 deaths were 3 breast cancer deaths and 1 lymphoid leukemia death. The authors claim that their results confirm "predictions of an increased cancer risk for the Eger hospital staff." They suggest an etiological role for EtO in the excess risk.

A.3.18. TOMPA ET AL. (1999)

The authors reported a cluster of 8 breast cancer cases and 8 other malignant tumor cases that developed over a period of 12 years in 98 nurses who worked in a hospital in the city of Eger, Hungary, and were exposed to EtO. These nurses were exposed for 5 to 15 years in a unit using gas sterilizer equipment. The authors report that EtO concentrations were in the neighborhood of 5 to 150 mg/m^3. The authors state that the high breast cancer incidence in the hospital in Eger indicates a combined effect of exposure to EtO and naturally occurring radioactive tap water, possibly due to the presence of radon. This case report study is discussed further in the genotoxicity section.

A.3.19. COGGON ET AL. (2004)

Descriptive information about this cohort is available from the earlier study (Gardner et al., 1989). This current update of the 1,864 men and 1,012 women described in the Gardner et al. study were followed to December 31, 2000. This added 13 more years of followup resulting in 565 observed deaths versus 607.6 expected. For total cancer, the observed number of deaths equaled 188 versus 184.2 expected. For NHL, 7 deaths were observed versus 4.8 expected. For leukemia, 5 deaths were observed versus 4.6 expected. All 5 leukemia deaths fell into the subset with definite or continual exposure to EtO, where only 2.6 were expected. In fact, the total number of deaths classified to the lymphohematopoietic cancer category was 17 with 12.9 expected. This increased risk was not significant. When definite exposure was established, the

authors found that the risk of lymphatic and hematopoietic cancer was increased with 9 observed deaths versus 4.9 expected. Deaths from leukemia were also increased in chemical workers with 4 leukemia deaths versus 1.7 expected. No increase was seen in the risk of hematopoietic cancer in the hospital sterilizing unit workers, who are mostly female. Another finding of little significance was that of cancer of the breast. Only 11 deaths were recorded in this cohort up to the cutoff date versus 13.1 expected. Since there were no female workers in the chemical industry, the results on breast cancer reflect only work in hospital sterilizing units. The researchers concluded that the risk of cancer must be low at the levels sustained by workers in Great Britain over the last 10 or 20 years.

A.4. SUMMARY

The initial human studies by Hogstedt et al. (1979a, b, 1986) and Hogstedt (1988), in which positive findings of leukemia and blood-related cancers suggested a causal effect, have been followed by studies that either do not indicate any increased risks of cancer or else suggest a dose-related increased risk of cancer at certain sites. These are chiefly cancers of the hematopoietic system and include leukemia, lymphosarcoma, reticulosarcoma and NHL. More recently, an association with breast cancer has also been suggested. However, the evidence is not conclusive because of inadequacies and limitations in the epidemiological database. The main effects and limitations are presented in Table A-5.

Exposure information, where available, indicates that levels of EtO probably were not high in these study cohorts. If a causal relationship exists between exposure to EtO and cancer, the reported EtO levels may have been too low to produce a significant finding. Exposures in the earlier years (prior to 1970) in most of the companies, hospitals, and other facilities where EtO was made or used are believed to have been in the range of 20 ppm, with excursions many times higher, although few actual measurements are available during this period. (One exception is the environmental study by Joyner (1964), who sampled airborne levels of EtO from 1960 to 1962 in a Texas City facility owned by Union Carbide.)

Almost all actual measurements of EtO were taken in the 1970s and 1980s at most plants and facilities in the U.S. and Europe, and levels have generally fallen to 5 ppm and below. Some plants may have never sustained high levels of airborne EtO. Assuming that there is a true risk of cancer associated with exposure to EtO, then the risk is not evident at the levels that existed in these plants except under certain conditions, possibly due to a lack of sensitivity in the available studies to detect associated cancers at low exposures.

The best evidence of a dose-response relationship comes from the NIOSH study of sterilizer workers by Steenland et al. (2004, 1991) and Stayner et al. (1993). This study estimated cumulative exposure (i.e., total lifetime occupational exposure to EtO) in every member of the

cohort. The investigators quantified exposure from the best available data on airborne levels of EtO throughout the history of the plants and used regression techniques to estimate individual EtO exposures. Industrial hygienists from NIOSH met with plant personnel to identify workers who were potentially exposed to EtO. An added advantage to this study, besides its diversity and size, is the absence of other known confounding exposures in the plants, especially benzene.

In the recent followup of the NIOSH cohort, as in the earlier study, Steenland et al. (2004) observed no overall excess of hematopoietic cancers (ICD-9 codes 200–208). In internal analyses, however, they found a significant positive trend (p=0.02) for hematopoietic cancers for males only, using log cumulative exposure and a 15-year lag, based on 37 male cases. In the Cox regression analysis using categorical cumulative exposure and a 15-year lag, a positive trend was observed and the OR in the highest exposure quintile was statistically significant (OR = 3.42; 95% CI 1.09–10.73). Similar results were obtained for the "lymphoid" category (lymphocytic leukemia, NHL, and myeloma). No evidence of a relationship between EtO exposure and hematopoietic cancers in females in this cohort was observed. The reasons for this discrepancy are unknown.

In the analysis by Teta et al. (1999) of UCC workers, the authors discussed the development of an age-dependent exposure history on each worker at the facility in West Virginia (Greenberg et al., 1990; Benson and Teta, 1993; Teta et al., 1993), based on departmental assignments and estimated exposure levels. Eight-hour TWA concentrations (ppm) were estimated over four time periods (1925–1939, 1940–1956, 1957–1973, and 1974–1978) at the two facilities in three exposure intensity categories (high, medium, low exposure departments) defined in the earlier study of the same two plants by Greenberg et al. Average exposures in the latter time period (1974–1978) were based on industrial hygiene monitoring conducted at the locations where the study subjects worked. Estimates for the earlier time periods were inferred from data on airborne exposure levels in "similar" manufacturing operations during the time periods of interest. These estimates are from the EtO production facility at Texas City studied by Joyner (1964) and the Swedish company described by Hogstedt et al. (1979b).

These inferred estimates of exposure formed the basis of the UCC dose-response assessment of the UCC study described in Teta et al. (1999). The authors fit several different models to the UCC exposure data and to the earlier NIOSH data (Stayner et al., 1993) and used Poisson regression techniques to estimate site-specific cancer risks for leukemia and "lymphoid" cancer. The results for leukemia were similar using either source of information (UCC or NIOSH) but were very different for "lymphoid" tumors due to the fact that none of the leukemia death certificates in the UCC study specified "lymphocytic" leukemia as the histologic type, whereas most of the NIOSH death certificates listed "lymphocytic" leukemia on the death certificate. The UCC data produced a "flat" relationship between ppm-years and the risk of

"lymphoid" cancer. The analysis of the NIOSH data produced an increased risk of "lymphoid" cancer with increasing exposure.

The many different analyses of the UCC data completed by Teta et al. (1999) are weakened by the reliance on inferred exposure data from other plants, mainly Joyner (1964) and Hogstedt et al. (1979a), which may not have been as similar as they assume to those for the employees of the two UCC plants that provided the basis of their own risk assessment. Although the workers at the Texas plant were all production workers, descriptions of the job processes at the UCC facilities in West Virginia lead one to believe that only a minority of the workers there were production workers, based on Teta et al. (1993, 1999). Most of the workers at the West Virginia facilities appear to have been employed in the use of EtO but not in the making of it.

Greenberg et al. (1990), in their partitioning of the job categories at the West Virginia facilities, considered production workers as "highly" exposed to EtO, whereas those who only used it were classified in a "medium" or "low" exposure category. Because of this potential difference in exposure between the two types of workers, it may not be appropriate to assume that the workers at the West Virginia facilities had "similar" exposures to the workers at the Texas plant prior to 1976. If, in fact, the workers at the West Virginia facilities had generally lower exposures, then risk calculations based on extrapolating levels from the Texas plant to the West Virginia plants could potentially underestimate the risk of cancer in those workers.

The NIOSH investigators developed estimates of exposure on the basis of knowledge and information developed from plant personnel at each of the 14 chemical plants in the cohort and meetings with NIOSH industrial hygienists. Furthermore, the NIOSH cohort was a much larger, more diversified group of workers who have been exposed to fewer confounders that might have skewed the findings. Hence, the Teta et al. (1999) exposure estimates are potentially less reliable than those of Steenland et al., despite the extensive risk assessment analyses and meta-analysis in Teta et al.

Although not explicitly citing any numbers, Teta et al. (1999) concluded that there was no evidence that EtO causes brain, stomach, or pancreatic cancer. They also concluded that their meta-analysis and tests of heterogeneity provide "compelling" evidence that the high risk of leukemia seen in the Hogstedt studies was an incorrect inference. They stated that findings for cancers of the lymphopoietic tissues (leukemia, NHL) were "inconclusive." Yet, in contrast, they concluded that EtO is a "probable human carcinogen," based partially on "limited evidence in humans."

One other study that provides cumulative exposure estimates is the incidence study by Hagmar et al. (1991, 1995). The short followup period and relative youthfulness of the cohort produced little morbidity by the end of the study, although some support for an excess risk of leukemia and lymphohematopoietic cancer had appeared.

In a separate analysis of the NIOSH cohort by Wong and Trent (1993), duration of exposure to EtO was used as a surrogate for exposure. These authors did not find any positive exposure-response relationships. They did observe an elevated significant risk of "NHL" in males (SMR = 2.47, $p<0.05$), based on 16 deaths, which was not dose- related or time-related. However, a deficit in females remained.

Increases in the risk of hematopoietic cancers or Hodgkin's lymphoma are also suggested in several other studies (Gardner et al., 1989; Coggon et al., 2004; Norman et al., 1995; Bisanti et al., 1993; Swaen et al., 1996; Olsen et al., 1997). However, in all these studies the deaths were few and the risk ratios were mostly nonsignificant except at higher estimated exposures or after long observation periods. They were not robust and there were potentially confounding influences, such as exposure to benzene and/or chlorohydrin derivatives.

In those plants where there were no detectable risks (Kiesselbach et al., 1990; Norman et al., 1995), the cohorts were relatively youthful or had not been followed for a sufficient number of years to observe any effects from exposure to EtO. In the study by Olsen et al. (1997), although a slight increase in the risk of cancer of the lymphopoietic and hematopoietic system was evident, the authors stated that their study provided some assurance that working in the chlorohydrin process had not produced significantly increased risks for pancreatic cancer or lymphopoietic or hematopoietic cancer, thus contradicting the findings of Benson and Teta (1993). This study lacks any measurement of airborne exposure to any of the chemicals mentioned and the authors indicated that an additional 5 to 10 years of followup would be needed to confirm the lack of a risk for the cancers described in their study.

Although the strongest evidence of a cancer risk is with cancer of the hematopoietic system, there are indications that the risk of stomach cancer may have been elevated in some studies (Hogstedt et al., 1979a, 1986; Kiesselbach et al., 1990; Teta et al., 1993); however, it attained significance only in the study by Hogstedt et al. (1979a), with 9 observed versus 1.27 expected. It was reported by Shore et al. (1993) that this excess may have been due to the fact that early workers at this plant "tasted" the chemical reaction product to assess the result of the EtO synthesis. This reaction mix would have contained ethylene dichloride and bis-chloroethyl ether. Ethylene dichloride is a suspected carcinogen, whereas bis-chloroethyl ether is not. This increased risk of stomach cancer was not supported by analyses of intensity or duration of exposure in the remaining studies, except that Benson and Teta (1993) suggested that exposure to this chemical increased the risk of pancreatic cancer and perhaps hematopoietic cancer but not stomach cancer.

A significant risk of pancreatic cancer first reported by Morgan et al. (1981) was also reported by Greenberg et al. (1990) in his cohort of chemical workers, but only in those workers assigned to the ethylene chlorohydrin production process, where the authors reported that

exposure to EtO was low. Benson and Teta (1993) attributed the increase in pancreatic cancer seen in Greenberg et al. (1990) to exposure to ethylene dichloride in the chlorohydrin process. However, Olson et al. (1997) refuted this finding in their study. The pancreatic cancers from the study by Morgan et al. (1981) also occurred in workers in a chlorohydrin process of EtO production. The possibility that exposure to a byproduct chemical such as ethylene dichloride may have produced the elevated risks of pancreatic cancer seen in these workers cannot be ruled out.

In addition to the cancer risks described above, some recent evidence indicates that exposure to EtO may increase the risk of breast cancer. The study by Norman et al. (1995) of women who sterilized medical equipment observed a significant twofold elevated risk of breast cancer, based on 12 cases. A study by Tompa et al. (1999) reported on a cluster of breast cancers occurring in Hungarian hospital workers exposed to EtO. In another Hungarian study of female hospital workers by Kardos et al. (2003), 3 breast cancers were noted out of 11 deaths reported by the authors. Although expected breast cancer deaths were not reported, the total expected deaths calculated was just slightly more than 4, making this a significant finding for cancer in this small cohort.

The most compelling evidence on breast cancer comes from the NIOSH cohort. In the recent update of this cohort, no overall excess of breast cancer mortality was observed in the female workers; however, a statistically significant SMR of 2.07 was observed in the highest cumulative exposure quartile, with a 20-year lag. In internal Cox regression analyses, a positive exposure-response (p=0.01) was observed for log cumulative exposure with a 20-year lag, based on 103 cases. Similar evidence of an excess risk of breast cancer was reported in a breast cancer incidence study of a subgroup of 7,576 female workers from the NIOSH cohort who were exposed for 1 year or longer (Steenland et al., 2003). A significant (p=0.002) linear trend in SIR was observed across cumulative exposure quintiles, with a 15-year lag. In internal Cox regression analyses, there was a significant regression coefficient with log cumulative exposure and a 15-year lag, based on 319 cases. Using categorical cumulative exposure, the OR of 1.74 was statistically significant in the highest exposure quintile. In a subcohort of 5,139 women with interviews, similar results were obtained based on 233 cases, and the models for this subcohort were also able to take information on other potential risk factors for breast cancer into account. Additionally, the coefficient for continuous cumulative exposure was also significant (p=0.02), with a 15-year lag.

Several other studies with female employees in the defined cohorts reported no increased risks of breast cancer due to exposure to EtO (Coggon et al., 2004; Hogstedt et al., 1986; Hagmar et al., 1991, 1995). However, these studies have much lower statistical power than the NIOSH studies, as evidenced by the much lower numbers of breast cancer cases that they report. The

largest number of cases in any of these other studies is 11 cases in the Coggon et al. (2004) study. Furthermore, none of these other studies conducted internal (or external) exposure-response analyses, which are the analyses that provided the strongest evidence in the NIOSH studies.

A.5. CONCLUSIONS

Experimental evidence demonstrates that exposure to EtO in rodents produces lymphohematopoietic cancers; therefore, an increase in the risk of lymphohematopoietic cancer in humans should not be unexpected. An increase in mammary gland carcinomas was also observed in mice. Although several human studies have indicated the possibility of a carcinogenic effect from exposure to EtO, especially for lymphohematopoietic cancers, the total weight of the epidemiologic evidence does not provide sufficient evidence to support a causative determination. The causality factors of temporality, coherence, and biological plausibility are satisfied. There is also evidence of consistency and specificity in the elevated risk of lymphohematopoietic cancer as a single entity in the human studies. The earlier significant risk of leukemia seen in the Hogstedt studies was supported in some studies and not in others. In fact, not all human studies of EtO have suggested an elevated risk of cancer and in those that do, the marginally elevated risks vary from one site to another within the lymphohematopoietic system. When combined under the rubric "lymphohematopoietic cancers," this loosely defined combination of blood malignancies produces a slightly elevated risk of cancer in some studies but not in all. There is evidence of a biological gradient in the significant dose-response relationship seen in the large, high-quality Steenland et al. (2004) study.

The best evidence of a carcinogenic effect produced by exposure to EtO is found in the NIOSH cohort of workers exposed to EtO in 14 sterilizer plants around the country (Steenland et al., 1991, 2004; Stayner et al., 1993). A positive trend in the risk of lymphohematopoietic and "lymphoid" neoplasms with increasing log cumulative exposure to EtO with a 15-year lag is evident. But there are some limitations to concluding that this is a causal relationship at this time. For example, there was a lack of dose-response relationship in females.

An elevated risk of lymphohematopoietic cancers from exposure to EtO is also apparent in several other studies. In some of these studies, confounding exposure to other chemicals produced in the chlorohydrin process concurrent with EtO may have been partially responsible for the excess risks. In other studies, where the chlorohydrin process was not present, there are no known confounding influences that would produce a positive risk of lymphohematopoietic cancer. Overall, the evidence on lymphohematopoietic cancers in humans is considered to be strong but not sufficient to support a causal association, i.e., limited.

There also exists the possibility that exposure to EtO may increase the risk of breast cancer, based chiefly on the Steenland et al. (2003, 2004) studies discussed earlier with some

corroborating evidence from the Norman et al. (1995) study of breast cancer in women exposed to EtO. The risk of breast cancer was narrowly analyzed in a few other studies (Hagmar et al., 1991; Hogstedt, 1988; Hogstedt et al., 1986; Coggon et al., 2004), and no increase in the risk of breast cancer was found. However, these studies had far fewer cases to analyze, 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 on internal exposure-response analyses. However, the authors suggest that the case is not conclusive of a causal association "due to inconsistencies in exposure-response trends and possible biases due to non-response and an incomplete cancer ascertainment." While these are not crippling limitations—exposure-response relationships are often not strictly monotonically increasing across finely dissected exposure categories, and the consistency of results between the full cohort (less nonresponse bias) and the subcohort with interviews (full case ascertainment) alleviates some of the concerns about those potential biases—we agree that the evidence for a causal association between breast cancer and EtO exposure is less than conclusive at this time.

Table A-5. Epidemiological studies of ethylene oxide and human cancer

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Sterilizers, production workers, Sweden Hogstedt et al., (1986); Hogstedt (1988)	709 (539 men, 170 women)	Plant 1: mean = 20 ppm in sterilizer room Plant 2: mean = 14 ppm in early years, less than 6 ppm later Plant 3: less than 8 ppm in early years, less than 2 ppm later	33 cancer deaths vs. 20 expected 7 leukemia deaths vs. 0.8 expected 10 stomach cancer deaths vs. 1.8 expected	Benzene, methyl formate, bis-(2-chloroethyl) ether, ethylene, ethylene chlorohydrin, ethylene dichloride, ethylene glycol, propylene oxide, amines, butylene oxide, formaldehyde, propylene, sodium	No personal exposure information from which to estimate dose No latency analysis Mixed exposure to other chemicals
Sterilizing workers in 8 hospitals and users in 4 companies, Great Britain Gardner et al. (1989)	2,876 (1,864 men, 1,012 women)	In early years, odor threshold of 700 ppm noted; in later years, 5 ppm or less was noted	3 leukemia deaths vs. 0.35 expected (after 20+ years latency) 5 esophageal cancer deaths vs. 2.2 expected 4 bladder cancer deaths vs. 2.04 expected 4 non-Hodgkin's lymphoma deaths vs. 1.6 expected 29 lung cancer deaths vs. 24.6 expected	Aliphatic and aromatic alcohols, amines, anionic surfactants, asbestos, butadiene, benzene, cadmium oxide, dimethylmine, ethylene, ethylene chlorohydrin, ethylene glycol, formaldehyde, heavy fuel oils, methanol, methylene chloride, propylene, propylene oxide, styrene, tars, white spirit, carbon tetrachloride	Insufficient followup Exposure classification scheme vague, making it difficult to develop dose-response gradient No exposure measure-ments prior to 1977, so individual exposure estimates were not made Mixed exposure to several other chemicals

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Coggon et al. (2004) Update of Gardner et al. (1989)	Same cohort followed addi-tional 13 years	Ibid.	<u>Recent Findings</u> 5 leukemia deaths vs. 2.6 expected (definite or continual exposure) 7 non-Hodgkin's lymphoma vs. 4.8 expected 11 breast cancers vs. 13.1 expected 17 hematopoietic cancers vs. 12.9 expected 9 lymphatic and/or hematopoietic cancers vs. 4.9 expected (definite exposure)	Ibid.	Ibid. and, in addition, no latency evaluation

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Production workers (methods unspecified) from 8 chemical plants in West Germany Kiesselbach et al. (1990)	2,658 men	No exposure information available	14 stomach cancer deaths vs. 10.1expected 3 esophageal cancer deaths vs. 1.5 expected 23 lung cancer deaths vs. 19.9 expected	Beta-naphthylamine, 4-amino-diphenyl, benzene, ethylene chlorohydrin, possibly alkylene oxide (ethylene oxide/propylene oxide), based on inclusion of plants that were part of a cohort study by Thiess et al. (1982)	Insufficient followup; few expected deaths in cancer sites of significance with which to analyze mortality Production methods not stated; information vague on what these plants do Latency analysis given only for total cancer and stomach cancer mortality Although categories of exposure are given, they are not based on actual measurements No actual measurement data are given; dose-response analysis is not possible

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Production workers and users at 2 chemical plants in West Virginia Greenberg et al. (1990)	2,174 men	Exposure prior to 1976 not known (estimates based on 1976 measurements and occurrence of medical conditions) 1–4.3 ppm TWA in later years	7 leukemia and aleukemia deaths vs. 3 expected; SMR = 2.3 3 liver cancer deaths vs. 1.8 expected; SMR = 1.7 7 pancreatic cancer deaths vs. 4.1 expected; SMR = 1.7 Suggestion of increasing risk of stomach cancer and leukemia/aleukemia with cumulative duration of potential exposure	Acetaldehyde, acetonitrile, acrolein, aldehydes, aliphatic and aromatic alcohols, alkanolamines, allyl chloride, amines, butadiene, benzene, bis-(chloroethyl) ether, ethylene dichloride, diethyl sulphate, dioxane, epichlorhydrin, ethylene, ethylene chlorohydrin, formaldehyde, glycol ethers, methylene chloride, propylene chlorohydrin, styrene, toluidine	Exceptionally low exposure levels to ethylene oxide, less than 1 ppm (from a 1976 survey) No actual measurements of exposure to ethylene oxide exist prior to 1976; inferences of levels of exposure to ethylene oxide at this plant were assumed to be similar to exposure levels measured at two other plants during early years (prior to 1976) Exposure occurred to many other chemicals, some of which may be carcinogenic Lack of quantitative estimates of individual exposure levels

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Same cohort as Greenberg et al. (1990) minus all chlorohydrin-exposed employees, followed an additional 10 years Teta et al. (1993)	1,896 men	Estimated exposure prior to 1956: 14+ ppm; after 1956: less than 10 ppm Prior to 1976 estimates were based on measurements taken at "similar" facilities	Trend of increasing risk of leukemia and aleukemia death with increasing duration of exposure	Same (except for chemicals specific to the chlorohydrin process)	Same
Only the chlorohydrin-exposed employees from Greenberg et al. (1990) cohort, followed an additional 10 years Benson and Teta (1993)	278 men	Reported to be very low exposure to ethylene oxide in the chlorohydrin process	8 pancreatic cancer deaths vs. 1.63 expected ($p<0.05$) 8 hematopoietic cancer deaths vs. 2.72 expected ($p<0.05$) SMR = 2.9	Same	Same

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Sterilizers of medical equipment and spices; and manufacturers and testers of medical sterilization equipment, in 14 plants in the United States Steenland et al. (1991); Stayner et al. (1993)	18,254 (45% male, 55% female)	1938–1976 (estimated): 16 ppm for sterilizer operators, 5 ppm for remainder 1977–1985 (mean): 4.3 for sterilizers, 2 ppm for remainder Individual cumulative exposure estimates calculated for workers in 13 of the 14 facilities	36 (lympho)hematopoietic cancer deaths vs. 33.8 expected 8 lymphosarcoma and reticulosarcoma deaths vs. 5.3 expected After 20+ years latency, SMR = 1.76 for hematopoietic cancer, a significant trend with increasing latency (p<0.03) Significantly increasing hematopoietic cancer and “lymphoid” cancer risks with cumulative exposure	No identified exposures to other chemicals	Potential bias due to lack of followup on “untraceable” members (4.5%) of the cohort Short duration of exposure and low median exposure levels Individual exposures were estimated prior to 1976 before first industrial hygiene survey was completed Short followup for most members of the cohort; only 8% had attained 20 years latency Little mortality (6.4%) had occurred in this large group of employees No exposure-response relationship among female workers

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Same cohort as Stayner et al. (1993) and Steenland et al. (1991), plus 474 additional members, followed 1 more year Wong and Trent (1993)	18,728 (45% male, 55% female)	Same as Steenland et al. (1991) and Stayner et al. (1993)	16 non-Hodgkin's lymphoma deaths in men vs. 6.47 expected 43 lymphohematopoietic cancer deaths observed vs. 42 expected (in men 32 observed vs. 22.2 expected) 14 other lymphatic cancer deaths vs. 11.4 expected (in men 11 observed vs. 5.8 expected) 14 leukemia deaths vs. 16.2 expected	No identifiable exposures to other chemicals	All of the limitations of Steenland et al. (1991) apply here Although this group is the same as Steenland et al. (1991), an additional unexplained 474 employees were added It is questionable that one additional year of followup added 392.2 expected deaths but only 176 observed deaths No effort was made to develop exposure-response data such as in Stayner et al. (1993) on the basis of individual cumulative exposure data but only on duration of employment

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Steenland et al. (2004) Update of Steenland et al. (1991), Stayner et al. (1993)	18,254 (45% male, 55% female)	Same as Steenland et al. (1991), with extension of worker histories based on job held at end of initial exposure assessment for those still employed at end of 1991 study (25% of cohort)	With 15-year lag, in internal Cox regression analyses, OR = 3.42 (p<0.05) in highest cumulative exposure group for (lympho)hematopoietic cancer in males; significant regression coefficient for continuous log cumulative exposure Similar results for "lymphoid" cancers in males For females, with 20-year lag, in internal Cox regression analyses, OR = 3.13 (p<0.05) for breast cancer mortality in highest cumulative exposure group; significant regression coefficient for continuous log cumulative exposure	No identified exposures to other chemicals	Potential bias due to lack of followup on "untraceable" members (4.5% of the cohort) Individual exposures were estimated prior to 1976 before first industrial hygiene survey was completed No increase in hematopoietic cancer risk with increase in exposure in women

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Women employees from Steenland et al. (2004) employed in commercial sterilization facilities for at least 1 year Steenland et al. (2003)	7,576 women	Same as in Steenland et al. (2004) Minimum of 1 year	SIR = 0.87 319 cases of breast cancer SIR = 0.94 20 in situ cases excluded A positive trend in SIRs with 15-year lag time for cumulative exposure (p=0.002) In internal nested case-control analysis, a positive exposure-response log of cumulative exposure with 15-year lag, top quintile had OR = 1.74, p<0.05 Similar results in subcohort of 5,139 women with interviews (233 cases)	Same as in Steenland et al. (2004), Stayner et al. (1993)	Interviews were available for only 68% of the women; thus, there is underascertainment of cancer cases. Also, there are potential nonresponse biases in the subcohort with interviews Exposure-response trends not strictly monotonically increasing

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Chemical workers licensed to handle ethylene oxide and other toxic chemicals, Italy Bisanti et al. (1993)	1,971 men	Levels were said to be high at beginning of employment; no actual measurements were available 637 workers were licensed only to handle ethylene oxide and no other toxic chemicals	43 total cancer deaths vs. 33 expected 6 hematopoietic cancer deaths vs. 2.4 expected 4 lymphosarcoma and reticulosarcoma deaths vs. 0.6 expected 5 hematopoietic cancer deaths vs. 0.7 expected in group licensed to handle only ethylene oxide	Toxic gases, dimethyl sulphate, methylene chloride, carbon disulphide, phosgene, chlorine, alkalic cyanides, sulfur dioxide, anhydrous ammonia, hydrocyanic acid	Lack of exposure data Insufficient followup for this young cohort Potential selection bias Possible earlier exposure than date of licensing would indicate
Two plants that produced disposable medical equipment, Sweden Hagmar et al. (1991, 1995)	2,170 (861 men, 1,309 women)	1964–1966, 75 ppm in sterilizers, 50 ppm in packers 1970–1972, 40 ppm in sterilizers, 20–35 ppm in packers and engineers By 1985, levels had dropped to 0.2 ppm in all categories except terilizers and to 0.75 ppm in sterilizers	6 lymphohematopoietic cancer cases vs. 3.37 expected Among subjects with at least 0.14 ppm-years of cumulative exposure and 10 years latency, the SIR for leukemia was 7.14, based on two cases	Fluorochlorocarbons, methyl formate (1:1 mixture with ethylene oxide)	Short followup period; authors recommend another 10 years of followup Youthful cohort—few cases and fewer deaths; unable to determine significance or relationships in categories Only a minority of subjects had high exposure to ethylene oxide

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Sterilizers of medical equipment and supplies that were assembled at this plant, New York Norman et al. (1995)	1,132 (204 men, 928 women)	In 1980, levels were 50–200 ppm (8-hr TWA); corrective action reduced levels to less than 20 ppm	Only 28 cancers were diagnosed 1 leukemia case vs. 0.54 expected 12 breast cancer cases vs. 4.7 expected (p<0.05) 2 pancreatic cancer cases vs. 0.51 expected	No other chemical exposures cited	Little power to detect any significant risk chiefly because a short followup period produced few cancer cases Insufficient latency analysis
Nested case-control study; cases and controls from a large chemical production plant, Belgium Swaen et al. (1996)	10 cases of Hodgkin's disease (7 cases confirmed) and 200 controls; all male	Cumulative exposure to ethylene oxide in cases was 500.2 ppm-months vs. 60.2 ppm-months in controls	3 cases indicated exposure to ethylene oxide, producing an OR = 8.5 (p<0.05)	Fertilizers, materials for synthetic fiber production, PVC, polystyrene, benzene, methane, acetone, ammonia, ammonium, sulfate, aniline, caprolactam, ethylene, Nah., oleum	This was a hypothesis-generating study; the authors were not looking for ethylene oxide exposure alone but for other chemical exposures as well to explain the excess risk Only one disease—Hodgkin's lymphoma—was analyzed

Table A-5. Epidemiological studies of ethylene oxide and human cancer (continued)

Population/ industry	Number of subjects	Extent of exposure to ethylene oxide	Health outcomes	Other chemicals to which subjects were potentially exposed	Limitations
Four ethylene oxide production plants in 3 states utilizing the chlorohydrin process (both ethylene and propylene) Olsen et al. (1997)	1,361 men	No actual measurements were taken	10 lymphohematopoietic cancer deaths vs. 7.7 expected After 24 years, the SMR increased to 1.44, based on 6 observed deaths No increase in pancreatic cancer	Bis-chloroethyl ether, propylene oxide, ethylene chlorohydrin, propylene chlorohydrin, ethylene dichloride, chlorohydrin chemicals	No actual airborne measurements of ethylene oxide or other chemicals such as ethylene dichloride were reported; only length of employment was used as a surrogate Increase in risk of lymphocytic and hematopoietic cancers after a 25-year latency is not shown in tabular form An additional 5 to 10 years of followup is needed to confirm the presence or lack of risk of pancreatic cancer and lymphopoietic and hematopoietic cancers
Female worker at Markhot Fereng Provincial hospital and clinic of Eger in the Pediatric Department Kardos et al. (2003)	299 female em-ployees	EtO sterilizing units with unknown elevated concentrations	11 cancer deaths observed compared with 4.38, 4.03, or 4.28 expected ($p<0.01$), based on comparison populations of Hungary, Heves County, and city of Eger, respectively	No identifiable exposures to other chemicals	Underlying cause of death provided on all 11 cases but no expected deaths available by cause Possible exposure to natural radium, which permeates the region

APPENDIX B: REFERENCES FOR FIGURE 3

The references in this list correspond to the additional data that was added to Figure 3 since the IARC (1994) genetic toxicity profile was published. See the Figure 3 legend for details.

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Appendix C. Extra risk calculation[a] for environmental exposure to 0.00608 ppm (the LEC_{01} for lymphohematopoietic cancer incidence in males)[b] using a linear exposure-response model based on the categorical cumulative exposure results of Steenland et al. (2004), with a 15-year lag, as described in Section 4.2.1.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality ($\times 10^5$/yr)	LH cancer incidence ($\times 10^5$/yr)	all cause hazard rate (h*)	prob of surviving interval (q)	prob of surviving up to interval (S)	LH cancer hazard rate (h)	cond prob of LH cancer incidence in interval	exp dur mid interval (xtime)	cum exp mid interval (xdose)	exposed LH cancer hazard rate (hx)	exposed all cause hazard rate (h*x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of LH cancer in interval
1	<1	801.5	4.1	0.0080	0.9920	1	0.00004	0.00004	0	0	0.00004	0.0080	0.9920	1	0.00004
2	1-4	38.5	10.1	0.0015	0.9985	0.9920	0.00040	0.00040	0	0	0.00040	0.0015	0.9985	0.9920	0.00040
3	5-9	19.2	5.4	0.0010	0.9990	0.9905	0.00027	0.00027	0	0	0.00027	0.0010	0.9990	0.9905	0.00027
4	10-14	25.3	5.5	0.0013	0.9987	0.9895	0.00028	0.00027	0	0	0.00028	0.0013	0.9987	0.9895	0.00027
5	15-19	96.3	8.0	0.0048	0.9952	0.9883	0.00040	0.00039	2.5	16.88	0.00041	0.0048	0.9952	0.9883	0.00040
6	20-24	137.6	10.4	0.0069	0.9931	0.9835	0.00052	0.00051	7.5	50.63	0.00054	0.0069	0.9931	0.9835	0.00053
7	25-29	138.5	12.2	0.0069	0.9931	0.9768	0.00061	0.00059	12.5	84.38	0.00065	0.0070	0.9931	0.9768	0.00063
8	30-34	161.0	15.6	0.0081	0.9920	0.9701	0.00078	0.00075	17.5	118.13	0.00085	0.0081	0.9919	0.9700	0.00082
9	35-39	211.1	19.4	0.0106	0.9895	0.9623	0.00097	0.00093	22.5	151.88	0.00108	0.0107	0.9894	0.9622	0.00104
10	40-44	302.9	26.2	0.0151	0.9850	0.9522	0.00131	0.00124	27.5	185.63	0.00149	0.0153	0.9848	0.9519	0.00141
11	45-49	455.8	33.9	0.0228	0.9775	0.9379	0.00170	0.00157	32.5	219.38	0.00198	0.0231	0.9772	0.9375	0.00183
12	50-54	654.6	49.7	0.0327	0.9678	0.9167	0.00249	0.00224	37.5	253.13	0.00296	0.0332	0.9673	0.9161	0.00267
13	55-59	1026.1	71.3	0.0513	0.9500	0.8872	0.00357	0.00308	42.5	286.88	0.00434	0.0521	0.9493	0.8862	0.00375
14	60-64	1595.9	102.1	0.0798	0.9233	0.8428	0.00511	0.00414	47.5	320.63	0.00635	0.0810	0.9222	0.8412	0.00513
15	65-69	2479.5	154.5	0.1240	0.8834	0.7782	0.00773	0.00565	52.5	354.38	0.00981	0.1261	0.8816	0.7757	0.00715
16	70-74	3816.5	204.1	0.1908	0.8263	0.6875	0.01021	0.00639	57.5	388.13	0.01322	0.1938	0.8238	0.6838	0.00822
17	75-79	5719.8	250.7	0.2860	0.7513	0.5680	0.01254	0.00619	62.5	421.88	0.01655	0.2900	0.7483	0.5633	0.00810
18	80-84	9156.8	286.2	0.4578	0.6326	0.4267	0.01431	0.00490	67.5	455.63	0.01927	0.4628	0.6295	0.4215	0.00650
							Ro =	0.03956						**Rx =**	0.04915

extra risk = (Rx-Ro)/(1-Ro) = 0.00998

column A: interval index number (i)
column B: 5-year age interval (except <1 and 1-4) up to age 85
column C: all-cause mortality rate for interval i ($\times 10^5$/year) (1999 data from NCHS; males)
column D: lymphohematopoietic cancer incidence rate for interval i ($\times 10^5$/year) (1996-2000 SEER data; males)[c]
column E: all-cause hazard rate for interval i (h^*_i) (= all-cause mortality rate × number of years in age interval)[d]
column F: probability of surviving interval i without being diagnosed with lymphohematopoietic cancer (q_i) (= $\exp(-h^*_i)$)
column G: probability of surviving up to interval i without having been diagnosed with lymphohematopoietic cancer (S_i) ($S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for i>1)
column H: lymphohematopoietic cancer incidence hazard rate for interval i (h_i) (= lymphohematopoietic cancer incidence rate × number of years in interval)

Appendix C. Extra risk calculation[a] for environmental exposure to 0.00608 ppm (the LEC_{01} for lymphohematopoietic cancer incidence in males)[b] using a linear exposure-response model based on the categorical cumulative exposure results of Steenland et al. (2004), with a 15-year lag, as described in Section 4.2.1. (continued)

column I: conditional probability of being diagnosed with lymphohematopoietic cancer in interval i (= $(h_i/h^*_i) \times S_i \times (1-q_i)$), i.e., conditional upon surviving up to interval i without having been diagnosed with lymphohematopoietic cancer [Ro, the background lifetime probability of being diagnosed with lymphohematopoietic cancer = the sum of the conditional probabilities across the intervals]

column J: exposure duration at mid-interval (taking into account 15-year lag) (xtime)

column K: cumulative exposure mid-interval (xdose) (= exposure level (i.e., 0.00608 ppm) × 365/240 × 20/10 × xtime × 365) [365/240 × 20/10 converts continuous environmental exposures to corresponding occupational exposures; xtime × 365 converts exposure duration in years to exposure duration in days]

column L: lymphohematopoietic cancer incidence hazard rate in exposed people for interval i (hx_i) (= $h_i \times (1 + \beta \times xdose)$, where $\beta = 0.000347 + (1.645 \times 0.000251) = 0.000760$) [0.000347 per ppm × day is the regression coefficient obtained from the weighted linear regression of the categorical results, dropping the highest exposure group (see Section 4.2.1.1). to estimate the LEC_{01}, i.e., the 95% lower bound on the continuous exposure giving an extra risk of 1%, the 95% upper bound on the regression coefficient is used, i.e., MLE + 1.645 × SE]

column M: all-cause hazard rate in exposed people for interval i (h^*x_i) (= $h^*_i + (hx_i - h_i)$)

column N: probability of surviving interval i without being diagnosed with lymphohmematopoietic cancer for exposed people (qx_i) (= $\exp(-h^*x_i)$)

column O: probability of surviving up to interval i without having been diagnosed with lymphohematopoietic cancer for exposed people(Sx_i) ($Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for i>1)

column P: conditional probability of being diagnosed with lymphohematopoietic cancer in interval i for exposed people (= $(hx_i/h^*x_i) \times Sx_i \times (1-qx_i)$) [Rx, the lifetime probability of being diagnosed with lymphohematopoietic cancer for exposed people = the sum of the conditional probabilities across the intervals]

[a] using the methodology of BEIR IV (1988)

[b] the estimated 95% lower bound on the continuous exposure level that gives a 1% extra lifetime risk of lymphohematopoietic cancer incidence in males

[c] background cancer incidence rates are used to estimate extra risks for cancer incidence under the assumption that the exposure-response relationship for cancer incidence is the same as that for cancer mortality (see Section 4.1.1.3)

[d] for the cancer incidence calculation, the all-cause hazard rate for interval i should technically be the rate of either dying of any cause or being diagnosed with the specific cancer during the interval, i.e., (the all-cause mortality rate for the interval + the cancer-specific incidence rate for the interval – the cancer-specific mortality rate for the interval [so that a cancer case isn't counted twice, i.e., upon diagnosis and upon death]) × number of years in interval. for the lymphohematopoietic cancer incidence calculations, this adjustment was ignored because the lymphohematopoietic cancer incidence rates are small when compared with the all-cause mortality rates. for the breast cancer incidence calculations, on the other hand, this adjustment was made in the all-cause hazard rate (see Section 4.1.2.3)

MLE: maximum likelihood estimate, SE: standard error

APPENDIX D: MODEL PARAMETERS IN THE ANALYSIS OF ANIMAL TUMOR INCIDENCE

Table D-1. Analysis of grouped data, NTP mice study (NTP, 1987)[a]; multistage model parameters

Tumor	Multistage[b] polynomial degree	q_0	q_1[c] $(mg/m^3)^{-1}$	q_2 $(mg/m^3)^{-2}$	q_3 $(mg/m^3)^{-2}$	*p* value (chi-square goodness of fit)
Males						
Lung adenomas plus carcinomas	1	2.52×10^{-1}	1.52×10^{-2}			0.92
Females						
Lung adenomas plus carcinomas	2	3.87×10^{-2}	0.0	4.80×10^{-4}		0.39
Malignant lymphoma	3	1.74×10^{-1}	0.0	0.0	1.13×10^{-5}	0.18
Uterine carcinoma	2	0.0	0.0	9.80×10^{-5}		0.90
Mammary carcinoma	1[d]	2.27×10^{-2}	1.09×10^{-2}			–

[a] The exposure concentrations were at 0, 50 ppm, and 100 ppm. These were adjusted to continuous exposure.
[b] $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$, where d is inhaled ethylene oxide exposure concentration.
[c] Even though q_1 is zero in some cases, the upper bound of q_1 is nonzero.
[d] The 100-ppm dose was deleted; the fit was perfect with only two points to fit.

Table D-2. Analysis of grouped data, Lynch et al. (1982, 1984) study of male F344 rats[a]; multistage model parameters

Tumor	Multistage[b] polynomial degree	q_0	q_1 $(mg/m^3)^{-1}$	*p* value (chi-square goodness of fit)
Splenic mononuclear cell leukemia	1[c]	3.12×10^{-1}	1.48×10^{-2}	–
Testicular peritoneal mesothelioma	1	3.54×10^{-2}	6.30×10^{-3}	0.34
Brain mixed-cell glioma	1	0	1.72×10^{-4}	0.96

[a] The exposure concentrations were at 0, 50 ppm, and 100 ppm. These were adjusted to continuous exposure.
[b] $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$, where d is inhaled ethylene oxide exposure concentration.
[c] The 100-ppm dose was deleted; the fit was perfect with only two points to fit.

Table D-3. Analysis of grouped data, Snellings et al. (1984) and Garman et al. (1985) reports on F344 rats[a]; multistage model parameters

Tumor	Multistage[b] polynomial degree	q_0	q_1 $(mg/m^3)^{-1}$	*p* value (chi-square goodness of fit)
Males				
Splenic mononuclear cell leukemia	1	1.63×10^{-1}	8.56×10^{-3}	0.34
Testicular peritoneal mesothelioma	1	2.38×10^{-2}	4.74×10^{-3}	0.68
Primary brain tumors	1	5.88×10^{-3}	2.92×10^{-3}	0.46
Females				
Splenic mononuclear cell leukemia	1	1.08×10^{-1}	2.37×10^{-2}	0.75
Primary brain tumors	1	5.94×10^{-3}	1.65×10^{-3}	0.80

[a] The exposure concentrations were at 0, 10 ppm, 33 ppm, and 100 ppm. These were adjusted to continuous exposure.

[b] $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)]$, where d is inhaled ethylene oxide exposure concentration.

Table D-4. Time-to-tumor analysis of individual animal data, NTP mice study (NTP, 1987)[a]; multistage-Weibull model[b] parameters

Tumor	Multistage polynomial degree	q_0	q_1 $(mg/m^3)^{-1}$	z
Males				
Lung adenomas plus carcinomas	1	3.44×10^{-1}	2.03×10^{-2}	5.39
Females				
Lung adenomas plus carcinomas	1	5.35×10^{-2}	1.76×10^{-2}	7.27
Malignant lymphoma	1	1.91×10^{-1}	8.80×10^{-3}	1.00
Uterine carcinoma	1	0.0	3.81×10^{-3}	3.93
Mammary carcinoma	1	3.78×10^{-2}	5.10×10^{-3}	1.00

[a] The exposure concentrations were at 0, 50 ppm, and 100 ppm. These were adjusted to continuous exposure.

[b] $P(d, t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$, where d is inhaled ethylene oxide exposure concentration.
The length of the study was 104 weeks. The times t and t_0 as expressed in the above formula are scaled so that the length of the study is 1.0. Then, q_0 is dimensionless, and the coefficients q_k are expressed in units of $(mg/m^3)^{-k}$.

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