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Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide

(CASRN 75-21-8)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

July 2013

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LIST OF ABBREVIATIONS

ADAF	age-dependent adjustment factor
AIC	Akaike information criterion
AIDS	acquired immune deficiency syndrome
AML	acute myeloid leukemia
AUC	areas under the curve
BEIR	Committee on the Biological Effects of Ionizing Radiation
CI	confidence interval
DSB	double-strand breaks
EC	effective concentration
EOIC	Ethylene Oxide Industry Council
EPA	U.S. Environmental Protection Agency
EtO	ethylene oxide
FRG	Federal Republic of Germany
GST	glutathione S-transferase
HAP	hazardous air pollutants
N7-HEG	N7-(2-hydroxyethyl)guanine
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IRIS	Integrated Risk Information System
LEC	lower confidence limit
MLE	maximum likelihood estimate
NCEA	National Center for Environmental Assessment
NHL	non-Hodgkin lymphoma
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
O^6-HEG	O^6-hydroxyethylguanine
OBS	observed number
OR	odds ratios
PBPK	physiologically based pharmacokinetic
POD	point of departure
RR	relative rate, i.e., rate ratio
SCE	sister chromatid exchanges
SE	standard error
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio
SMR	standard mortality ratios
TWA	time-weighted average
UCC	Union Carbide Corporation
UCL	upper confidence limit
WHO	World Health Organization

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This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix H.

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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 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 most (but not all) of the epidemiological studies of EtO-exposed workers, manifested as an increase either in leukemia or in cancer of the lymphoid tissue. Of note, in one large epidemiologic study conducted by the National Institute for Occupational Safety and Health (NIOSH) of sterilizer workers that had a well-defined exposure assessment for individuals, positive exposure-response trends were reported for lymphohematopoietic cancer mortality, primarily in males and in particular for lymphoid cancer (i.e., non-Hodgkin lymphoma, myeloma, and lymphocytic leukemia), and for breast cancer mortality in females (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). There is supporting evidence for an association between EtO and breast cancer from other studies, but the database is more limited than that for lymphohematopoietic cancers.

Although the evidence of carcinogenicity from human studies was deemed short of conclusive on its own, EtO is characterized as "carcinogenic to humans" by the inhalation route of exposure based on the total weight of evidence, in accordance with EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). The lines of evidence supporting this characterization include: (1) strong, but less than conclusive on its own, epidemiological evidence of lymphohematopoietic cancers and breast cancer in EtO-exposed workers, (2) extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure, (3) clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity, and (4) strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome

damage in humans exposed to EtO. Overall, there is strong confidence in the hazard characterization of EtO as "carcinogenic to humans."

This document describes the derivation of inhalation unit risk estimates for cancer mortality and incidence based on the human data from the large NIOSH study (Steenland et al., 2004; 2003). This study was selected for the derivation of risk estimates because it was the largest of the available studies and it had exposure estimates for the individual workers from a high-quality exposure assessment. Multiple modeling approaches were evaluated for the exposure-response data, including modeling the cancer response as a function of either categorical exposures or continuous individual exposure levels. Preferred approaches were defined for each cancer endpoint in consideration of both the statistical properties and biological reasonableness of the resulting model forms (see Tables 4-4 and 4-12 for a summary of models investigated in this assessment for lymphoid cancer and breast cancer incidence, respectively, and the considerations used in model selection).

Under the common assumption that relative risk is independent of age, an LEC_{01} (lower 95% confidence limit on the EC_{01}, the estimated effective concentration associated with 1% extra risk) was calculated using a life-table analysis and linear modeling of the categorical Cox regression analysis results for excess lymphoid cancer mortality (Steenland et al., 2004; additional results for both sexes combined provided by Dr. Steenland in Appendix D) excluding the highest exposure group to mitigate the supralinearity of the exposure-response data. Linear low-dose extrapolation below the range of observations is supported by the conclusion that a mutagenic mode of action is operative in EtO carcinogenicity. Linear low-dose extrapolation from the LEC_{01} for lymphoid cancer mortality yielded a lifetime extra cancer unit risk estimate of 2.2×10^{-4} per $\mu g/m^3$ (4.0×10^{-4} per ppb)[1] of continuous EtO exposure. Applying the same linear regression coefficient and life-table analysis to background lymphoid cancer *incidence* rates and applying linear low-dose extrapolation resulted in a preferred lifetime extra lymphoid cancer unit risk estimate of 4.8×10^{-4} per $\mu g/m^3$ (8.8×10^{-4} per ppb), as cancer incidence estimates are generally preferred over mortality estimates.

Using the same approach, a unit risk estimate of 2.8×10^{-4} per $\mu g/m^3$ (5.1×10^{-4} per ppb) was derived from the breast cancer mortality results of the same epidemiology study (Steenland et al., 2004). Breast cancer incidence risk estimates, on the other hand, were calculated from the data from a breast cancer incidence study of the same occupational cohort (Steenland et al., 2003), and, for these data, a two-piece linear spline model was used for the exposure-response modeling. Using the same life-table approach and linear low-dose extrapolation, a unit risk estimate of 9.5×10^{-4} per $\mu g/m^3$ (1.7×10^{-3} per ppb) was obtained for breast cancer incidence.

[1]Conversion equation: 1 ppm = 1830 $\mu g/m^3$.

Again, the incidence estimate is preferred over the mortality estimate. Combining the incidence risk estimates for the two cancer types resulted in a total cancer unit risk estimate of 1.2×10^{-3} per $\mu g/m^3$ (2.3×10^{-3} per ppb).

Unit risk estimates were also derived from the three chronic rodent bioassays for EtO reported in the literature. These estimates, ranging from 2.2×10^{-5} per $\mu g/m^3$ to 4.6×10^{-5} per $\mu g/m^3$, are over 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 sizeable difference between the rodent-based and the human-based estimates, 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 estimates based on the human data are the preferred estimates for this assessment.

Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and as there are no chemical-specific data from which to assess early-life susceptibility, increased early-life susceptibility should be assumed, according to 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). This mode-of-action-based assumption of increased early-life susceptibility supersedes the assumption of age independence under which the human-data-based estimates presented above were derived. Thus, using the same approach as for the estimates discussed above but initiating exposure in the life-table analysis at age 16 instead of at birth, adult-exposure-only unit risk estimates were calculated from the human data under an alternate assumption that relative risk is independent of age for adults, which represent the life stage for which the data upon which the exposure-response modeling was conducted pertain. These adult-exposure-only unit risk estimates were then rescaled to a 70-year basis for use in the standard ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios. The resulting adult-based unit risk estimates were 4.35×10^{-4} per $\mu g/m^3$ (7.95×10^{-4} per ppb) for lymphoid cancer incidence, 8.21×10^{-4} per $\mu g/m^3$ (1.50×10^{-3} per ppb) for breast cancer incidence in females, and 1.08×10^{-3} per $\mu g/m^3$ (1.98×10^{-3} per ppb) for both cancer types combined. For exposure scenarios involving early-life exposure, the age-dependent adjustment factors (ADAFs) should be applied, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b). Applying the ADAFs to obtain a full lifetime total cancer unit risk estimate yields 1.8×10^{-3} per $\mu g/m^3$ (3.3×10^{-3} per ppb), and the commensurate lifetime chronic (lower-bound) exposure level of EtO corresponding to an increased cancer risk of 10^{-6} is 0.0006 $\mu g/m^3$ (0.0003 ppb).

The major sources of uncertainty in the unit risk estimates derived from the human data include the low-dose extrapolation, the retrospective exposure assessment conducted for the epidemiology study, and the exposure-response modeling of the epidemiological data (see Section 4.1.4 for a discussion of these and other sources of uncertainty in the unit risk estimates).

Although there are uncertainties in the unit risk estimate, confidence in the estimate is relatively high. First, there is strong confidence in the hazard characterization of EtO as "carcinogenic to humans," which is based on strong epidemiological evidence supplemented by other lines of evidence. Second, the unit risk estimate is based on human data from a large, high-quality epidemiology study with individual worker exposures estimated using a high-quality regression model. Finally, the use of low-exposure linear extrapolation is strongly supported by the conclusion that EtO carcinogenicity has a mutagenic mode of action.

Confidence in the unit risk estimate is particularly high for the breast cancer component, the largest contributor to the total cancer unit risk estimate, which is based on over 200 incident cases for which the investigators had information on other potential breast cancer risk factors. The selected model for the breast cancer incidence data was the best-fitting model of the models investigated as well as the model which provided the best representation of the categorical results, particularly in the lower exposure range of greatest relevance for the derivation of a unit risk estimate. Alternate estimates calculated from other reasonable models suggest that a unit risk estimate for breast cancer incidence fourfold lower (corresponding to a total cancer unit risk estimate of twofold lower) is plausible; however, unit risk estimates notably lower than that are considered unlikely from the available data.

There is lower confidence in the lymphoid cancer component of the unit risk estimate because it is based on fewer events (40 lymphoid cancer deaths); incidence risk was estimated from mortality data; and the exposure-response relationship is exceedingly supralinear, such that continuous models yield apparently implausibly steep low-exposure slopes. Although these continuous models provided statistically significant slope coefficients, there was low confidence in such steep slopes, which, particularly for the two-piece spline models, are highly dependent on a small number of cases in the low-exposure range. Thus, a linear regression model of the categorical results for the lowest three quartiles was used to derive the unit risk estimate for lymphoid cancer, and there was greater confidence in the more moderate slope resulting from that model, although it was not statistically significant, because it was based on more data and provided a good representation of the categorical results across this larger data range in the lower-exposure region. So, while there is lower confidence in the lymphoid cancer unit risk estimate than in the breast cancer unit risk estimate, the lymphoid cancer estimate is considered a

reasonable estimate from the available data, and overall, there is relatively high confidence in the total cancer unit risk estimate.

The unit risk estimate is intended to provide a reasonable upper bound on cancer risk. The estimate was developed for environmental exposure levels (it is considered valid for exposures up to 140 $\mu g/m^3$ [75 ppb]) and is not applicable to higher-level exposures, such as may occur occupationally, which appear to have a different exposure-response relationship. However, occupational exposure levels of EtO are of concern to EPA when EtO is used as a pesticide (e.g., sterilizing agent or fumigant). Therefore, this document also presents extra risk estimates for the two cancer types for a range of occupational exposure scenarios (see Section 4.7). Maximum likelihood estimates of the extra risk of lymphoid cancer and breast cancer combined for the range of occupational exposure scenarios considered (i.e., 0.1 to 1 ppm 8-hour TWA for 35 years) ranged from 0.047 to 0.14. The overall uncertainty associated with the extra risk estimates for occupational exposure scenarios is less than that associated with the unit risk estimates for environmental exposures. The extra risk estimates are derived for occupational exposure scenarios that yield cumulative exposures well within the range of the exposures in the NIOSH study. Moreover, the NIOSH study is a study of sterilizer workers who used EtO for the sterilization of medical supplies or spices (Steenland et al., 1991); thus, the results are directly applicable to workers in these occupations, and these are among the occupations of primary concern for current occupational EtO exposures.

Table 1-1 provides a summary of the major findings in this assessment.

Table 1-1. Summary of major findings

Hazard Conclusions	
Hazard Characterization	The weight of evidence from epidemiological studies and supporting information is sufficient to conclude that ethylene oxide is carcinogenic to humans.
Mode of Action	The weight of evidence is sufficient to conclude that ethylene oxide carcinogenicity has a mutagenic mode of action.
Unit Risk Estimates (for environmental exposures)[a]	
Basis	**Inhalation unit risk estimate[a] (per μg/m^3)[b]**
Full lifetime unit risk estimate[c]	
Total cancer risk based on human data—lymphoid cancer incidence and breast cancer incidence in females	**1.80×10^{-3}**
Adult-based unit risk estimates[d]	
Total cancer risk based on human data—lymphoid cancer incidence and breast cancer incidence in females	**1.08×10^{-3}**
Lymphoid cancer incidence in both sexes based on human data	4.35×10^{-4}
Breast cancer incidence in females based on human data	8.21×10^{-4}
Total cancer risk based on human data—lymphoid cancer incidence and range of female breast cancer incidence estimates from three alternate models	$5.64 \times 10^{-4} – 1.08 \times 10^{-3}$
Total cancer incidence risk estimate from rodent data (female mouse)	4.6×10^{-5}
Extra risk estimates for occupational exposure scenarios (see Section 4.7)	
Maximum likelihood estimates of the extra risk of lymphoid cancer and breast cancer combined for the range of occupational exposure scenarios considered (i.e., 0.1 to 1 ppm 8-hr TWA for 35 yr)	**0.047–0.14**

[a]These unit risk estimates are not intended for use with continuous lifetime exposure levels above about 140 μg/m^3. See Section 4.7 for risk estimates based on occupational exposure scenarios. Preferred estimates are in bold.

[b]To convert unit risk estimates to (ppm)$^{-1}$, multiply the (μg/m^3)$^{-1}$ estimates by 1,830 (μg/m^3)/ppm.

[c]Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and because of the lack of chemical-specific data, EPA assumes increased early-life susceptibility and recommends the application of ADAFs, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b), for exposure scenarios that include early-life exposures. For the full lifetime (upper bound) unit risk estimate presented here, ADAFs have been applied, as described in Section 4.4.

[d]These (upper bound) unit risk estimates are intended for use in ADAF calculations and less-than-lifetime adult exposure scenarios (U.S. EPA, 2005b). Note that these are not the same as the unit risk estimates derived directly from the human data in Section 4.1 under the assumption that RRs are independent of age. Under that assumption, the key unit risk estimates were 4.8×10^{-4} per μg/m^3 for lymphoid cancer incidence, 9.5×10^{-4} per μg/m^3 for breast cancer incidence, and 1.2×10^{-3} per μg/m^3 for the combined cancer incidence risk from those two cancers. See Section 4.4 for the derivation of the adult-based unit risk estimates.

2. INTRODUCTION

The purpose of this document is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to carcinogenicity from chronic inhalation exposure to ethylene oxide (EtO) (CASRN 75-21-8). It is not intended to be a comprehensive treatise on the chemical or toxicological nature of EtO. In general, this IRIS Carcinogenicity Assessment provides information on the carcinogenic hazard potential of EtO and quantitative estimates of risk from inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates for inhalation exposure (inhalation unit risks) are derived. The definition of an inhalation unit risk is a plausible upper bound on the estimate of risk per $\mu g/m^3$ air breathed.

Development of the hazard identification and dose-response assessments for EtO has followed the general guidelines for risk assessment as set forth by the National Research Council (NRC, 1983). United States Environmental Protection Agency (U.S. EPA) Guidelines and Risk Assessment Forum Technical Panel Reports that were used in the development of this assessment include the following: *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), *Benchmark Dose Technical Guidance* (U.S. EPA, 2012), *Science Policy Council Handbook*: *Risk Characterization*(U.S. EPA, 2000), *Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), and *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2006b).

An earlier external review draft of this carcinogenicity assessment (U.S. EPA, 2006a) was peer reviewed by a panel of EPA's Science Advisory Board (SAB) in 2007 (SAB, 2007). This revised external review draft is being released for public comment and for additional external peer review to receive comments primarily on the expanded exposure-response modeling of certain epidemiologic data done in response to comments from the 2007 SAB review.

The literature search strategy first employed for this assessment was based on the Chemical Abstracts Service Registry Number (CASRN) and at least one common name. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. References have been added after the first external peer review in response to the reviewers' and public comments. References have also been added for completeness. These references have not changed the overall qualitative or

quantitative conclusions. See Appendix I for a list of the references added after the first external peer review. The cutoff date for literature inclusion into this carcinogenicity assessment was 30 June 2010. A systematic literature search was conducted for the time frame from January 2006 to May 2013 to ensure that no major studies were missed from the time of the first external review draft in 2006 until the cutoff date and to determine if any significant new studies had been published since the cutoff date that might alter the findings of the assessment. This systematic literature search is described in Appendix J. No new studies were identified that would impact the assessment's major conclusions. Nonetheless, two new studies of high pertinence to the assessment have been published since the cutoff date for literature inclusion, and these studies are reviewed briefly in Appendix J for transparency and completeness. The references considered and cited in this document, including abstracts, can be found on the Health and Environmental Research Online (HERO) website.[2]

On 23 December 2011, the Consolidated Appropriations Act, 2012, was signed into law.[3] The report language included direction to EPA for the IRIS Program related to recommendations provided by the National Research Council (NRC) in their review of EPA's draft IRIS assessment of formaldehyde. The NRC's recommendations, provided in Chapter 7 of their review report, offered suggestions to EPA for improving the development of IRIS assessments. The report language included the following:

> The Agency shall incorporate, as appropriate, based on chemical-specific datasets and biological effects, the recommendations of Chapter 7 of the National Research Council's Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde into the IRIS process … For draft assessments released in fiscal year 2012, the Agency shall include documentation describing how the Chapter 7 recommendations of the National Academy of Sciences (NAS) have been implemented or addressed, including an explanation for why certain recommendations were not incorporated.

Consistent with the direction provided by Congress, documentation of how the recommendations from Chapter 7 of the NRC report have been implemented in this assessment

[2]HERO is a database of scientific studies and other references used to develop EPA's risk assessments, which are aimed at understanding the health and environmental effects of pollutants and chemicals. HERO is developed and managed in EPA's Office of Research and Development (ORD) by the National Center for Environmental Assessment (NCEA). The database includes more than 750,000 scientific articles from the peer-reviewed literature. New studies are added continuously to HERO.

[3]Pub. L. No. 112-74, Consolidated Appropriations Act, 2012.

is provided in Appendix K. This documentation also includes an explanation for why certain recommendations were not incorporated.

For general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

3. HAZARD IDENTIFICATION

This chapter presents the evidence considered in the hazard identification of EtO carcinogenicity and the hazard characterization resulting from the weight-of-evidence evaluation. Section 3.1 summarizes the human evidence (a more detailed discussion of the human cancer studies is presented in Appendix A). Section 3.2 describes the evidence from experimental animal studies. Section 3.3 discusses supporting evidence, in particular evidence regarding the genotoxicity of EtO. Section 3.4 provides the mode-of-action analysis for EtO carcinogenicity. To conclude the chapter, Section 3.5 presents the hazard characterization for EtO carcinogenicity and a discussion of life stages and populations with potentially increased susceptibility.

3.1. EVIDENCE OF CANCER IN HUMANS

The literature from 1988 to present contains numerous epidemiological 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 discussed in more detail and critically reviewed in Appendix A. Table A-5 in Appendix A provides a tabular summary of the epidemiological studies, including some study details, results, and limitations. The strengths and weaknesses of these studies were evaluated individually using standard considerations in evaluating epidemiological studies. The major areas of concern are study design, exposure assessment, and data analysis. General features of study design considered include sample size and assessment of the health endpoint. For case-control studies, design considerations include representativeness of cases, selection of controls, participation rates, use of proxy respondents, and interview approach (e.g., blinding). For cohort studies, design considerations include selection of referent population (e.g., internal comparisons are generally preferred to comparisons with an external population), loss to follow-up, and length of follow-up. Exposure assessment issues include specificity of exposure (exposure misclassification), characterization of exposure (e.g., ever exposed or quantitative estimate of exposure level), and potential confounders. Analysis considerations include adjustment for potential confounders or effect modifiers and modeling of exposure-response relationships.

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

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 was 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, there are 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 follow-up 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 lymphoma (2 vs. 1 expected), non-Hodgkin 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 about 2,000 male workers who were assigned to operations that used or produced EtO in either of two Union Carbide Corporation (UCC) chemical production facilities in West Virginia (Valdez-Flores et al., 2010; Swaen et al., 2009; Teta et al., 1999; Benson and Teta, 1993; Teta et al., 1993; Greenberg et al., 1990) have been published. EtO was produced at these facilities until 1971, after which it was imported to the facilities. For EtO production, the chlorohydrin process was used from 1925 to 1957, and the direct oxidation process was used from 1937 to 1971 (during overlapping years, both processes were in use). The cohort was observed from 1940 through 1978 in the original study (Greenberg et al., 1990), through 1988 in the Teta et al. (1999); Teta et al. (1993) and Benson and Teta (1993) studies, and through 2003 in the latter two studies. A large-scale industrial hygiene survey and monitoring of EtO concentrations was carried out in 1976, at which time EtO was in use at the facilities but no longer in production.

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 (note that the chlorohydrin production unit produced primarily ethylene chlorohydrin, which is used in chlorohydrin-based EtO production, but this unit is not where chlorohydrin-based EtO production took place). Limitations of this study included multiple exposures to many different chemicals in the facility through the years and lack of EtO exposure measurements prior to 1976. Three categories of exposure were established for analysis—low, intermediate, and high—based on a qualitative characterization of the potential for EtO exposure. The number of workers in each exposure category was not reported. No significant findings of a dose-response relationship were discernible. No quantitative estimates of individual exposure were made in this study, and no latency analysis was conducted (average follow-up was 20 years). Furthermore, EtO is not the only chemical to which the observed excesses in cancer mortality could be attributed.

A follow-up study (Teta et al., 1993) that extended the observation of this cohort (excluding the 278 chlorohydrin production unit workers, who reportedly had low EtO exposures) 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 ($p = 0.28$) and was based on only five cases. The

average follow-up was 27 years, and at least 10 years had elapsed since first exposure for all workers. The same problems of exposure ascertainment exist for this study as for that of Greenberg et al. (1990), and furthermore, the follow-up did not update work histories for the workers after 1978. EtO production at the plants was discontinued before 1978, as noted by Teta et al. (1993); however, according to Greenberg et al. (1990), certain nonproduction areas had "intermediate" potential for EtO exposure, although estimates of exposure levels suggest that the levels would also be lower during the update period [<1 ppm 8-hour time-weighted average (TWA), according to Teta et al. (1993)]. It appears from the Greenberg et al. (1990) publication that the high potential exposure group was reserved for EtO production workers, and according to Teta et al. (1993), there were only 425 EtO production workers in the cohort. Of these, only 118 worked in the chlorohydrin-based production process, where exposures were reportedly highest. Essentially, the study did not support the earlier studies of cancer in EtO workers; however, it was limited by low statistical power and a crude exposure assessment and, thus, is not very informative regarding whether exposure to EtO is causally related to cancer.

In a parallel follow-up study through 1988 of only the chlorohydrin production employees, Benson and Teta (1993) found that pancreatic cancer and lymphohematopoietic cancer cases continued to accumulate and that the SMRs were statistically significant for pancreatic cancer (SMR = 4.9; Obs = 8, $p < 0.05$) and for lymphohematopoietic cancer (SMR = 2.9; Obs = 8, $p < 0.05$). These investigators 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 (see Table A-5 in Appendix A). Furthermore, the chlorohydrin production unit was reportedly considered a low potential EtO exposure department. Hence this study has little weight in determining the carcinogenicity of EtO.

In a later analysis, Teta et al. (1999) fitted Poisson regression dose-response models to the UCC data (followed through 1988 and excluding the chlorohydrin production workers) and to data (followed through 1987) from a study by the National Institute for Occupational Safety and Health (NIOSH) (described below). Because Teta et al. (1999) did not present risk ratios for the cumulative exposure categories used to model the 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. However, the models are based on small numbers of cases (16 [5 UCC, 11 NIOSH] for leukemia; 22 [3 UCC,

19 NIOSH] for lymphoid cancers), and no statistics are provided to assess model goodness-of-fit or to compare across models. In any event, this analysis is superseded by the more recent analysis by the same authors (Valdez-Flores et al., 2010) of the results of more recent follow-up studies of these cohorts (see below).

Swaen et al. (2009) studied the same UCC cohort identified by Teta et al. (1993), i.e., without the chlorohydrin production workers, but extended the cohort enumeration period from the end of 1978 to the end of 1988, identifying 167 additional workers, and conducted mortality follow-up of the resulting cohort of 2,063 male workers through 2003. Work histories were also extended through 1988 (exposures after 1988 were considered negligible compared to earlier exposure levels). Swaen et al. (2009) used an exposure assessment based on the qualitative categorizations of potential EtO exposure in the different departments developed by Greenberg et al. (1990) and time-period exposure estimates from Teta et al. (1993). This exposure assessment was relatively crude, based on just a small number of department-specific and time-period-specific categories, and with exposure estimates for only a few of the categories derived from actual measurements (see Appendix A.2.20 for details).

At the end of the 2003 follow-up, 1,048 of the 2,063 workers had died (Swaen et al., 2009). The all-cause mortality SMR was 0.85 (95% CI = 0.80, 0.90) and the cancer SMR was 0.95 (95% CI = 0.84, 1.06). None of the SMRs for specific cancer types showed any statistically significant increases. In analyses stratified by hire date [pre- (inclusive) or post-1956], the SMR for leukemia was elevated but not statistically significant (1.51; 95% CI 0.69, 2.87) in the early-hire group, based on nine deaths. In analyses stratified by duration of employment, no trends were apparent for any of the lymphohematopoietic cancers, although in the 9+ years of employment subgroup, the SMR for NHL was nonsignificantly increased (1.49; 95% CI 0.48, 3.48), based on five deaths. In SMR analyses stratified by cumulative exposure, no trends were apparent for any of the lymphohematopoietic cancers and there were no notable elevations for the highest cumulative exposure category. Note that only 27 lymphohematopoietic cancer deaths (including 12 leukemias and 11 NHLs) were observed in the cohort.

Swaen et al. (2009) also did internal Cox proportional hazards modeling for some disease categories (all-cause mortality, leukemia mortality, and lymphoid cancer [NHL, lymphocytic leukemia, and myeloma] mortality [17 deaths]), using cumulative exposure as the exposure metric. These analyses showed no evidence of an exposure-response relationship. Alternate Cox proportional hazard analyses and categorical exposure-response analyses of the UCC data conducted by Valdez-Flores et al. (2010) for a larger set of cancer endpoints similarly reported an absence of any exposure-response relationships. Each of these cancer analyses, however,

relies on small numbers of cases and a crude exposure assessment, where there is a high potential for exposure misclassification.

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 evaluating the carcinogenicity of EtO.

NIOSH conducted an industry-wide study of 18,254 workers (45% male and 55% female) in 14 plants where EtO was used (Steenland et al., 2004; Stayner et al., 1993; Steenland et al., 1991). Most of the workers were exposed while sterilizing medical supplies and treating spices and in the manufacture and testing of medical sterilizers. Individual exposure estimates were derived for workers from 13 of the 14 plants. 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). Briefly, a regression model was developed, allowing the estimation of exposure levels for time periods, facilities, and operations for which industrial hygiene data were unavailable. The data for the model consisted of 2,700 individual time-weighted exposure values for workers' personal breathing zones, acquired from 18 facilities between 1976 and 1985. The data were divided into two sets, one for developing the regression model and the second for testing it. Seven out of 23 independent variables tested for inclusion in the regression 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. (See Appendix A, Section A.2.8, for more details on the NIOSH exposure assessment and its evaluation.) Results of the original follow-up study through 1987 are presented in Steenland et al. (1991) and Stayner et al. (1993). The cohort averaged 26.8 years of follow-up in the extended follow-up study through 1998, and 16% of the cohort had died (Steenland et al., 2004).

The overall SMR for cancer was 0.98, based on 860 deaths (Steenland et al., 2004). The SMR for (lympho)hematopoietic cancer was 1.00, based on 79 cases. Exposure-response analyses, however, revealed exposure-related increases in hematopoietic cancer mortality risk, although the effect was primarily in males, when analyzed by sex. In categorical life-table analysis, men with >13,500 ppm-days of cumulative exposure had an SMR of 1.46 (Obs = 13). In internal Cox regression analyses (i.e., analyses in which the referent population is within the

cohort) with exposure as a continuous variable, statistically significant trends in males for all 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.[4] 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 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; Obs = 13). Internal exposure-response analyses also noted a significant positive trend for breast cancer mortality using the log of cumulative exposure and a 20-year lag time ($p = 0.01$). In internal categorical analyses, a statistically significant OR for breast cancer mortality was observed in the highest cumulative exposure quartile with a 20-year lag (OR = 3.13; 95% CI = 1.42–6.92).

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 dose-response assessment. It possesses more attributes than the others for performing risk analysis (e.g., good-quality estimates of individual exposure, lack of exposure to other chemicals, and a large and diverse cohort of workers).

It should be noted that Steenland et al. (2004) used Cox regression models, which are log-linear relative rate models, thus providing some low-dose sublinear curvature for doses expressed in terms of cumulative exposure. However, the best-fitting dose-response model for both male lymphoid cancers and male all hematopoietic cancers was for dose expressed in terms of log cumulative exposure, indicating supralinearity of the low-dose data. Supralinearity of the

[4]The sex difference is not statistically significant, however, and the trends for both sexes combined are also statistically significant [$p = 0.01$ and $p = 0.02$, respectively; see Tables D-3e and D-4e in Appendix D].

dose-response data was also indicated by the categorical exposure results. 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 follow-up period by 1 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 = 6; $p < 0.05$). 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.

Valdez-Flores et al. (2010) conducted alternative Cox proportional hazards modeling and categorical exposure-response analyses using data from the UCC cohort (Swaen et al., 2009), the NIOSH cohort (Steenland et al., 2004) and the two cohorts combined, analyzing the sexes both separately and together. These investigators reported that they found no evidence of exposure-response relationships for cumulative exposure with either the Cox model or categorical analyses for all of the cohort/endpoint data sets examined (endpoints included all lymphohematopoietic cancers, lymphoid cancers, and female breast cancer, the latter in the NIOSH cohort only). Valdez-Flores et al. (2010) did observe statistically significant increases in response rates in the highest exposure quintile relative to the lowest exposure quintile for lymphohematopoietic and lymphoid cancers in males in the NIOSH cohort, consistent with the categorical results of Steenland et al. (2004), as well as a statistically significant increase in the highest exposure quintile for lymphoid cancers in males and females combined in the NIOSH cohort, consistent with the results in Appendix D. Because the exposure assessment conducted for the UCC cohort is much cruder (see above and Appendix A.2.20), especially for the highest exposures, than the NIOSH exposure assessment (which was based on a validated regression model; see Appendix A.2.8), EPA considers the results of exposure-response analyses of the combined cohort data to have greater uncertainty than those from analyses of the NIOSH cohort alone, despite the additional cases contributed by the UCC cohort (e.g., the UCC cohort

contributes 17 cases of lymphoid cancer to the 53 from the NIOSH cohort). Furthermore, Valdez-Flores et al. (2010) did not use any log cumulative exposure models, and these were the models that were statistically significant in the Steenland et al. (2004) analyses, consistent with the apparent supralinearity of the NIOSH exposure-response data. See Appendix A.2.20 for a more detailed discussion of the Valdez-Flores et al. (2010) analyses and how they compared with the Steenland et al. (2004) analyses.

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 the study's usefulness for establishing the carcinogenicity of EtO.

Hagmar et al. (Hagmar et al., 1995; Hagmar et al., 1991) 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 cumulative exposures 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 follow-up time was short (median 11.8 years), and only a small fraction of the workers was highly exposed, the report is suggestive of an association between EtO exposure and hematopoietic cancers. The risk of breast cancer was less than expected, although with such short follow-up, the total numbers of cases was small (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 lymphoma 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 dose-response assessment.

Olsen et al. (1997) studied 1,361 male employees working in the ethylene and propylene chlorohydrin production and processing areas located within the EtO and propylene oxide production plants at four Dow Chemical Company sites in the United States. Although these investigators found a nonsignificant positive trend between duration of employment as

chlorohydrin workers and lymphohematopoietic cancer (Obs = 10), they concluded that there was no appreciable risk in these workers, in contrast to 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 studies was also an incidence study. The follow-up 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 1 month.

Tompa et al. (1999) reported a cluster of eight breast cancers and eight 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 Surveillance, Epidemiology, and End Results (SEER) reference rates for comparison. Results with the full cohort are expected to be underestimated, however, because of case under-ascertainment in the women without interviews. A significant exposure-response trend was observed for SIR across cumulative exposure quintiles, using a 15-year lag time ($p = 0.002$). In internal Cox regression analyses, with exposure as a continuous variable, a significant trend for breast cancer incidence was obtained for log cumulative exposure with a 15-year lag ($p = 0.05$), taking age, race, and year of birth into account. Using duration of exposure, lagged 15 years, provided a slightly better fit ($p = 0.02$), while models with cumulative (nontransformed), 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 for breast cancer incidence 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 between EtO exposure and breast cancer incidence 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 imprecision 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 RR estimates cannot be determined. However, the observation of 3 breast cancer deaths, with at most 4.4 (with Hungarian national rates as the referent) total cancer deaths expected, is indicative of an increased risk of breast cancer[5], and this characterization is supported by the reference of Major et al. (2001) to a cluster of breast cancer cases in female nurses at the same hospital.

[5]Hungarian age-standardized female cancer mortality rates reported by the International Agency for Research on Cancer (http://eu-cancer.iarc.fr/country-348-hungary.html,en) suggest that the ratio of breast cancer deaths to total cancer deaths in Hungarian females is about 0.16 (28.0/100,000 breast cancer mortality rate versus 180.0/100,000 total cancer mortality rate). Although a comparison of this general population ratio with the ratio of 0.68 for breast cancer to total cancer mortality in the Kardos et al. (2003) study is necessarily crude because the general population ratio is not based on the age-standardized rates that would correspond to the age distribution of the person-time of the women in the study, which are unknown, the large difference between the ratios (0.68 for the study versus 0.16 for the general population) indicates an increased risk of breast cancer in the study.

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 eight relevant criteria of causality envisioned by Hill (1965), temporality, coherence, biological plausibility, and analogy 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, most of the relative risk estimates are not large (strong) in magnitude. See Section 3.5.1 for a more detailed discussion of the Hill criteria as applied to the EtO database.

The large NIOSH study (Steenland et al., 2004; Stayner et al., 1993; Steenland et al., 1991) of workers at 14 chemical plants around the country provides the strongest evidence of carcinogenicity. A statistically significant positive trend was observed in the risk of lymphohematopoietic neoplasms with increasing (log) cumulative exposure to EtO, although the results for this model were reported only for males (the sex difference is not statistically significant, however, and the trend for both sexes combined is statistically significant; see Appendix D). Despite limitations in the data, most other epidemiologic studies have also found elevated risks of lymphohematopoietic cancer from exposure to EtO (summarized briefly in Section 3.1 and Table 3-1; see also Appendix A for more details, in particular Table A-5 for a summary of study results and limitations). 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. Moreover, the studies that do not report a significant lymphohematopoietic cancer effect from exposure to EtO have major limitations, such as small numbers of cases and inadequate exposure information (see Table A-5 in Appendix A).

In addition, there is evidence of an increase in the risk of both breast cancer mortality and incidence in women who are exposed to EtO. Studies have reported increases in the risk of breast cancer in women employees of commercial sterilization plants (Steenland et al., 2004; Steenland et al., 2003; 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 (Coggon et al., 2004; Hagmar et al., 1991) or breast cancer results were not reported (Hogstedt, 1988; Hogstedt et al., 1986). However, these studies had far fewer cases to analyze than the NIOSH studies, and most did not have individual exposure estimates and relied on external comparisons (see Table 3-2 for a brief summary and Table A-5 in Appendix A for more details). The Steenland et al. (2004) and

Table 3-1. Epidemiological studies of ethylene oxide and human cancer—lymphohematopoietic cancer results[a]

Study/Population/ Industry	Number of subjects	Lymphohematopoietic cancer results				Comments
Hogstedt (1988) and Hogstedt et al. (1986). Sterilizers, production workers, Sweden.	709 (539 men, 170 women)	*cancer deaths* leukemia (ICD-8 204-207) lymphohematopoietic (ICD-8 200-208)	*observed* 7 9	*expected* 0.8 2.0	*SMR (95% CI)* 9.2 (3.7, 19)[b] 4.6 (2.1, 8.7)[b]	Insufficient follow-up; only 12.0% of cohort had died (85 deaths). Exposure to other chemicals.
Coggon et al. (2004). Update of Gardner et al. (1989). Sterilizing workers in 8 hospitals and users in 4 companies, Great Britain.	2,876 (1,864 men, 1,012 women)	*cancer deaths* leukemia (ICD-9 204-208) leukemia (definite or continual exposure) NHL (ICD-9 200+202) lymphohematopoietic (ICD-9 200-208)	*observed* 5 5 7 17	*expected* 4.6 2.6 4.8 12.9	*SMR (95% CI)* 1.1 (0.35, 2.5) 1.9 (0.62, 4.5)[b] 1.5 (0.58, 3.0)[b] 1.3 (0.77, 2.1)[b]	Short follow-up; only 19.6% of cohort had died (565 deaths). Exposure to other chemicals.
Kiesselbach et al. (1990). Production workers (methods unspecified) from 8 chemical plants in West Germany.	2,658 men	*cancer deaths* leukemia (ICD-9 204-208) lymphohematopoietic (ICD-9 200-208)	*observed* 2 5	*expected* 2.35 5	*SMR (95% CI)* 0.85 (0.10, 3.1) 1.0 (0.32, 2.3)	Insufficient follow-up; only 10.1% of cohort had died (268 deaths). Exposure to other chemicals.
Benson and Teta (1993). Follow-up of only the chlorohydrin-exposed employees from Greenberg et al. (1990) cohort. Production workers at a chemical plant in West Virginia.	278 men	*cancer deaths* leukemia and aleukemia lymphosarcoma and reticulosarcoma lymphohematopoietic (ICD NS)	*observed* 4 1 8	*expected* 1.14 0.50 2.72	*SMR (95% CI)* 3.5 (0.96, 8.9) 2.0 (0.05, 11) 2.9 (1.3, 5.8)	EtO exposures reported to be low in the chlorohydrin process. Exposure to other chemicals. Very small cohort; thus, small numbers of specific cancers despite long follow-up (52.9% had died; 147 deaths).

Table 3-1. Epidemiological studies of ethylene oxide and human cancer—lymphohematopoietic cancer results[a] (continued)

Study/Population/ Industry	Number of subjects	Lymphohematopoietic cancer results	Comments
Swaen et al. (2009). Update of Teta et al. (1993) [Greenberg et al. (1990) cohort minus all chlorohydrin-exposed employees] plus cohort enumeration extended an additional 10 years, adding 167 workers. Production workers and users at 2 chemical plants in West Virginia.	2,063 men	*cancer deaths* — *observed* — *expected* — *SMR (95% CI)* leukemia — 11 — 11.8 — 0.93 (0.47, 1.7) leukemia (in workers hired before 1956) — 9 — NR — 1.5 (0.69, 2.9) NHL — 12 — 11.5 — 1.05 (0.54, 1.8) lymphohematopoietic (ICD NS) — 27 — 30.4 — 0.89 (0.59, 1.3) *Internal Cox regression analyses:* No statistically significant trends were observed for lymphoid or leukemia cancer categories for continuous cumulative exposure.	Small cohort; thus, small numbers of specific cancers even though long follow-up time (50.8% had died; 1,048 deaths). Crude exposure assessment, especially for the early time periods. Exposure to other chemicals.
Steenland et al. (2004). Update of Steenland et al. (1991), Stayner et al. (1993). Sterilizers of medical equipment and spices; and manufacturers and testers of medical sterilization equipment, in 14 plants in the United States.	18,254 (45% male, 55% female)	*cancer deaths* — *observed* — *expected* — *SMR (95% CI)* leukemia (ICD-9 204-208) — 29 — NR — 0.99 (0.71, 1.36) NHL (ICD-9 200+202) — 31 — NR — 1.00 (0.72, 1.35) lymphohematopoietic (ICD-9 200-208) — 79 — NR — 1.00 (0.79, 1.24) *Internal Cox regression analyses:* "lymphoid" cancers (ICD-9 200, 202, 203, 204): OR = 3.0 (p = 0.046) in highest cumulative exposure group, with 15-yr lag; significant regression coefficient for continuous log cumulative exposure (p = 0.02). lymphohematopoietic cancer (ICD-9 200-208): OR = 2.96 (p = 0.03) in highest cumulative exposure group, with 15-yr lag; significant regression coefficient for continuous log cumulative exposure (p = 0.009).	Large cohort; thus, substantial number of deaths (2,852) despite short follow-up (15.6% had died). High-quality exposure assessment. No evidence of exposure to other occupational carcinogens. No increase in lymphohematopoietic cancer risk with increase in exposure in women. Results from internal Cox regression analyses for both sexes combined from Sections D.3 and D.4 of Appendix D.

Table 3-1. Epidemiological studies of ethylene oxide and human cancer—lymphohematopoietic cancer results[a] (continued)

Study/Population/ Industry	Number of subjects	Lymphohematopoietic cancer results				Comments
Bisanti et al. (1993). Chemical workers licensed to handle EtO and other toxic chemicals, Italy.	1,971 men	*cancer deaths*	*observed*	*expected*	*SMR (95% CI)*	Insufficient follow-up; only 3.9% of cohort had died (76 deaths). Exposure to other chemicals.
		leukemia (ICD-9 204-208)	2	1.0	1.9 (0.23, 7.0)	
		lymphosarcoma and reticulosarcoma (ICD-9 200)	4	0.6	6.8 (1.9, 17)	
		lymphohematopoietic (ICD-9 200-208)	6	2.4	2.5 (0.91, 5.5)	
		in group only licensed to handle EtO (n = 637):				
		leukemia	2	0.3	6.5 (0.79, 23)	
		lymphosarcoma and reticulosarcoma	3	0.2	17 (3.5, 50)	
		lymphohematopoietic	5	0.7	7.0 (2.3, 16)	
Hagmar et al. (1995) and Hagmar et al. (1991). Two plants that produced disposable medical equipment, Sweden.	2,170 (861 men, 1,309 women)	*cancer cases*	*observed*	*expected*	*SIR (95% CI)*	Short follow-up period (only 40 cancer cases).
		leukemia (ICD-7 204-205)	2	0.82	2.4 (0.30, 8.8)	
		NHL (ICD-7 200+202)	2	1.25	1.6 (0.19, 5.8)	
		lymphohematopoietic (ICD-7 200-209)	6	3.37	1.8 (0.65, 3.9)	
		leukemia	2	0.28	7.1 (0.87, 26)	
		(among subjects with at least 0.14 ppm-years of cumulative exposure and 10 years latency)				
Norman et al. (1995). Sterilizers of medical equipment and supplies that were assembled at this plant, New York.	1,132 (204 men, 928 women)	*cancer cases*	*observed*	*expected*	*SIR (95% CI)*	Short follow-up period and small cohort (only 28 cancer cases).
		leukemia (ICD NS)	1	0.54	1.85 (0.05, 10)[b]	
Swaen et al. (1996). Nested case-control study; cases and controls from a large chemical production plant, Belgium.	10 cases of Hodgkin lymphoma (7 confirmed) and 200 controls; all male	*cancer*			*OR (95% CI)*	Hypothesis-generating study to investigate a cluster of Hodgkin lymphomas observed at a chemical plant. Exposure to other chemicals.
		Hodgkin lymphoma (ICD 201)			8.5 (1.4, 40)	

Table 3-1. Epidemiological studies of ethylene oxide and human cancer—lymphohematopoietic cancer results[a] (continued)

Study/Population/ Industry	Number of subjects	Lymphohematopoietic cancer results				Comments
Olsen et al. (1997). Four EtO production plants (chlorohydrin process) in 3 states.	1,361 men	*cancer deaths*	*observed*	*expected*	*SMR (95% CI)*	Short follow-up and small cohort; thus, small numbers of specific cancers (22.0% had died; 300 deaths). Exposure to other chemicals.
		leukemia (ICD-8 204-207)	2	3.0	0.67 (0.08, 2.4)	
		lymphosarcoma and reticulosarcoma (ICD-8 200)	1	1.1	0.91 (0.02, 5.1)	
		lymphohematopoietic (ICD-8 200-209)	10	7.7	1.3 (0.62, 2.4)	
Kardos et al. (2003). Female workers from pediatric clinic of hospital in Eger, Hungary.	299 women	1 lymphoid leukemia death of 11 cancer deaths; expected number not reported.				Short follow-up period and small cohort (only 11 cancer deaths). Possible exposure to natural radium, which permeates the region.

[a]Extracted from Table A-5 of Appendix A, with addition of some summary results (e.g., SMRs).
[b]Calculated by EPA assuming Poisson distribution.
ICD NS: ICD codes not specified; NR: not reported

Table 3-2. Summary of epidemiological results on EtO and breast cancer (all sterilizer workers)[a]

Study	Number of Women	Breast Cancer Results	Comments
Hogstedt (1988); Hogstedt et al. (1986) Swedish incidence and mortality study	170	not reported	Only 8 deaths (7 from cancer) had occurred among the women. 37 incident cancer cases (27 expected) in the total cohort (including 539 men); 7 were lymphohematopoietic cancers, rest not reported.
Coggon et al. (2004) Great Britain mortality study	1,011 women hospital workers	*exposure category* *observed* *expected* *SMR (95% CI)* continual 5 7.2 intermittent 0 0.7 unknown 6 5.2 ALL 11 13.1 1.04 (0.42, 1.51)	11 breast cancer deaths. only 14% of the cohort of 1,405 (including males) hospital workers had died.
Steenland et al. (2004) U.S. mortality study	9,908	SMR in highest quartile of cumulative exposure (with 20-yr lag) = 2.07 ($p < 0.05$). significant Cox regression coefficient for log cumulative exposure (20-yr lag) ($p = 0.01$).	103 breast cancer deaths.
Steenland et al. (2003) U.S. breast cancer incidence study	7,576 employed for ≥1 yr; 5,139 with interviews	*full cohort results*: Cox regression analysis OR = 1.74 (95% CI: 1.16, 2.65) for highest cumulative exposure quintile (15-yr lag). $p = 0.05$ for regression coefficient with log cumulative exposure (15-yr lag). *subcohort results*: Cox regression analysis OR = 1.87 (95% CI: 1.12, 3.10) for highest cumulative exposure quintile (15-yr lag). $p = 0.02$ for regression coefficient with cumulative exposure (15-yr lag); $p = 0.03$ with log cumulative exposure (15-yr lag).	319 cases in full cohort. 233 cases in subcohort with interviews.

Table 3-2. Summary of epidemiological results on EtO and breast cancer (all sterilizer workers)[a] (continued)

Study	Number of Women	Breast Cancer Results	Comments
Hagmar et al. (1995) and Hagmar et al. (1991) Swedish cancer incidence study	1,309	5 cases vs. 10.8 expected SIR = 0.46 (95% CI: 0.15, 1.08).	5 cases.
Norman et al. (1995) U.S. cancer incidence study	928	SIRs ranged from 1.72 (95% CI: 0.99, 3.00) to 2.40 (95% CI: 1.32, 4.37) depending on calendar year of follow-up, assumptions about completeness of follow-up, and reference rates used.	12 cases.
Kardos et al. (2003) Hungarian mortality study	299	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; 3 were breast cancer deaths, i.e., 3 breast cancer deaths vs. ~4.3 total deaths expected. Although the expected number of breast cancer deaths was not reported, the number of breast cancer deaths observed for the total deaths expected is indicative of an increased risk of breast cancer (see footnote 2 in Section 3.1).	3 deaths.

[a]Extracted from Table A-5 of Appendix A

Steenland et al. (2003) 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 human 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 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 primarily 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 more recent finding.

3.2. EVIDENCE OF CANCER IN LABORATORY ANIMALS

The International Agency for Research on Cancer (IARC) monograph (IARC, 1994b) 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, 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., 1984a; Lynch et al., 1984b) in males; (Garman et al., 1986, 1985; Snellings et al., 1984), 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 observed in both sexes. These data are summarized in Table 3-3. 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. [Lynch et al. (1984a); Lynch et al. (1984b)] 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. (1984a) 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 (see Table 3-4). 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 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.

Table 3-3. 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[d]	6.94 (4.51)	2.22×10^{-2}
Females					
Lung adenomas plus Carcinomas	2/44	5/44	22/49[e]	14.8 (9.12)	1.1×10^{-2}
Malignant Lymphoma	9/44	6/44	22/49[f]	21.1 (13.9)	7.18×10^{-3}
Uterine Carcinoma	0/44	1/44	5/49[g]	32.8 (23.1)	4.33×10^{-3}
Mammary carcinoma[h]	1/44	8/44[f]	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 hr/d, 5 d/wk; 1 ppm = 1.83 mg/m^3.
[c]Calculated using Tox_Risk program.
[d]$p < 0.01$ (pairwise Fisher's exact test).
[e]$p < 0.001$ (pairwise Fisher's exact test).
[f]$p < 0.05$ (pairwise Fisher's exact test).
[g]$p = 0.058$ by pairwise Fisher's exact test compared to concurrent controls; however, uterine carcinomas are rare tumors in female $B6C3F_1$ mice, and $p < 0.0001$ by pairwise Fisher's exact test compared to the NTP historical control incidence of 1/1,077 for inhalation (air) female $B6C3F_1$ mice fed the NIH-07 diet.
[h]Highest dose was deleted in order to fit a model to the dose-response data.

Table 3-4. Tumor incidence data in Lynch et al. (1984a; 1984b) 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[d]	30/76	7.11 (3.94)	$2.54 \times 10^{-2.}$
Testicular peritoneal mesothelioma	3/78	9/79	21/79[e]	16.7 (11.8)	$8.5 \times 10^{-3.}$
Brain mixed-cell glioma	0/76	2/77	5/79[e]	65.7 (37.4)	$2.68 \times 10^{-3.}$

[a]Adjusted to continuous exposure from experimental exposure conditions of 7 hr/d, 5 d/wk; 1 ppm = 1.83 mg/m^3.
[b]Calculated using Tox_Risk program.
[c]Highest dose deleted while fitting the dose-response data.
[d]$p < 0.05$ (pairwise Fisher's exact test).
[e]$p < 0.01$ (pairwise Fisher's exact test).

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. (1984) claim that it is unlikely that the viral outbreak contributed to the EtO-associated tumor findings. After the outbreak, mortality rates returned to preoutbreak 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 3-5. Note that these investigators observed the same types of tumors (splenic leukemia and peritoneal mesothelioma) seen by Lynch et al. (1984a); Lynch et al. (1984b). 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. (1984) 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., 1986, 1985), both males and females had a concentration-dependent increased incidence of brain tumors (see Table 3-5). Garman et al. (1986, 1985) report incidences including all rats from the 18- and 24-month kills and all rats 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 Laboratory Animals

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

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 (Fennell and Brown, 2001; Csanady et al., 2000; Brown et al., 1998; Brown et al., 1996).

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 3-1): (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. (1998); Brown et al. (1996). 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

Table 3-5. 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[c]	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})[d] (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[f] (32%)	9/30[f] (30%)	12.3 (6.43)	1.56×10^{-2}
Testicular peritoneal mesothelioma	2/97 (2.1%)	2/51 (3.9%)	4/39 (10%)	4/30[f] (13%)	22.3 (11.6)	8.66×10^{-3}
Primary brain tumors	1/181 (0.55%)	1/92 (1.1%)	5/85[f] (5.9%)	7/87[g] (8.1%)	36.1 (22.3)	4.5×10^{-3}
Females						
Splenic mononuclear cell leukemia	11/116 (9.5%)	11/54[f] (21%)	14/48[g] (30%)	15/26[h] (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[f] (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 hr/d, 5 d/wk; 1 ppm = 1.83 mg/m^3.
[c]Results for both control groups combined.
[d]Using Tox_Risk program.
[e]Numbers in parentheses indicate percentage incidence values.
[f]$p < 0.05$ (pairwise Fisher's exact test).
[g]$p < 0.01$ (pairwise Fisher's exact test).
[h]$p < 0.001$ (pairwise Fisher's exact test).

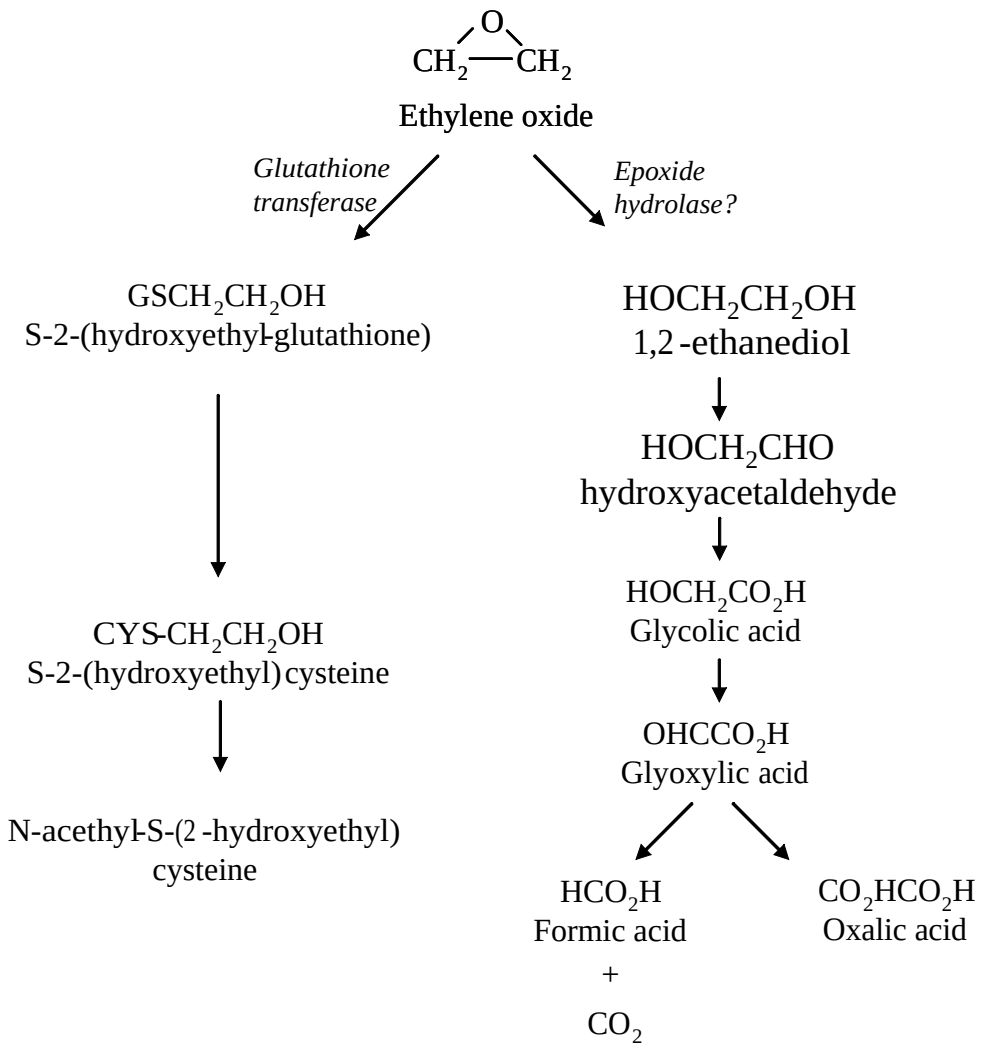

Figure 3-1. Metabolism of ethylene oxide.

elimination half-life in humans is 42 minutes (Filser et al., 1992), and the half-life in salt water is 4 days (IARC, 1994b).

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. 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 the metabolism and disappearance of EtO is primarily a result of glutathione conjugation, but at higher concentrations, when tissue glutathione begins to be depleted, the elimination occurs via a

slower nonenzymatic 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 3-2). 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).

3.3.2. Protein Adducts

EtO forms DNA (see Section 3.3.3.1) and hemoglobin adducts within tissues throughout the body (Walker et al., 1992a; Walker et al., 1992b). Formation of hemoglobin adducts has been used as a measure of exposure to EtO. The main sites of alkylation are cysteine, histidine, and the N-terminal valine; however, for analytical reasons, the N-(2-hydroxyethyl)valine adduct is generally preferred for measurements (Walker et al., 1990). Walker et al. (1992b) reported measurements of this hemoglobin adduct and showed how the concentration of the adducts changes according to the dynamics of red blood cell turnover. Walker et al. (1992b) measured hemoglobin adduct formation in mice and rats exposed to 0, 3, 10, 33, 100, and 300 (rats only) ppm of EtO (6 hours/day, 5 days/week, for 4 weeks). Response was linear in both species up to 33 ppm, after which the slope significantly increased. The exposure-related decrease in glutathione concentration in liver, lung, and other tissues observed by Brown et al. (1998) in mice is a plausible explanation for the increasing rate of hemoglobin adduct formation at higher exposures.

In humans, hemoglobin adducts can be used as biomarkers of recent exposure to EtO (IARC, 2008a; Boogaard, 2002; IARC, 1994b), and several studies have reported exposure-response relationships between hemoglobin adduct levels and EtO exposure levels (e.g., van Sittert et al., 1993; Schulte et al., 1992). Hemoglobin adducts are good general indicators of exposure because they are stable (DNA adducts, on the other hand, may be repaired

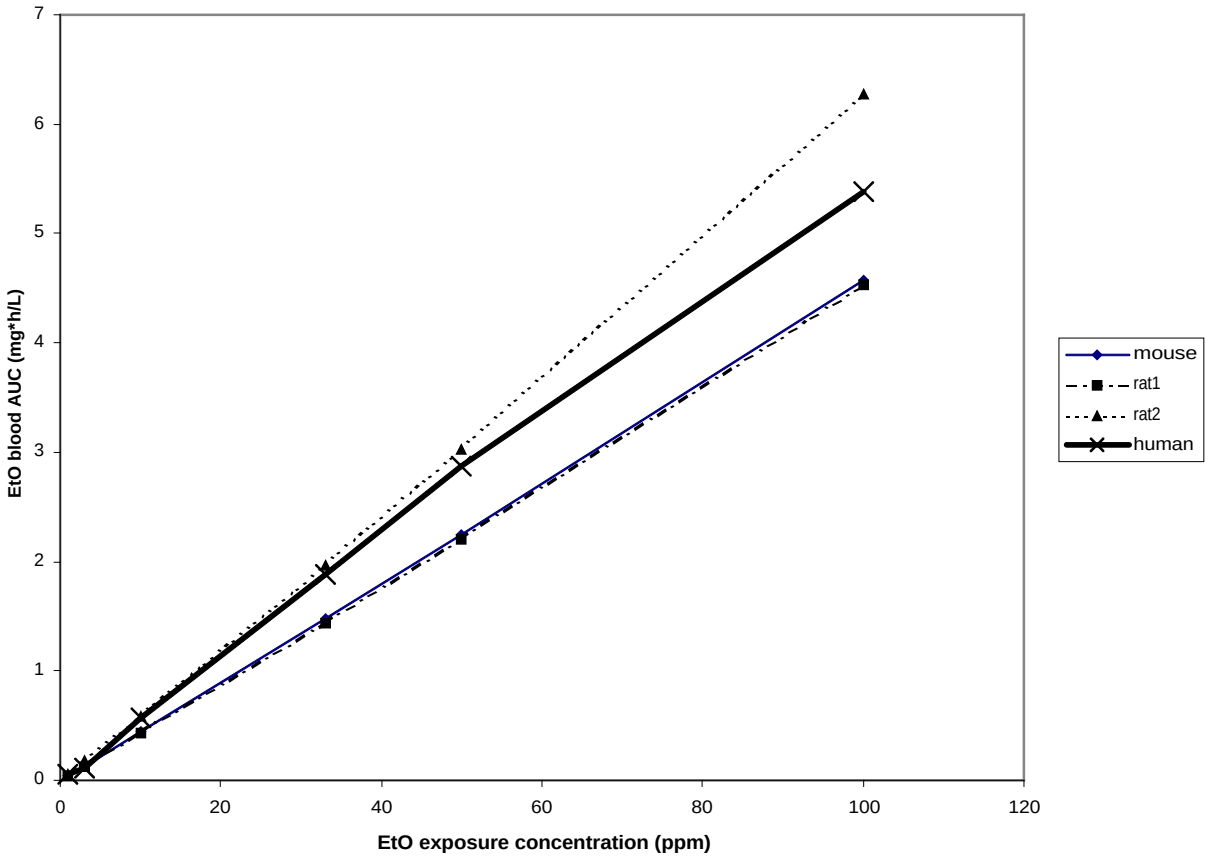

Figure 3-2. Simulated blood AUCs for EtO following a 6-hour exposure to EtO from the rat, mouse, and human PBPK models of Fennell and Brown (2001); based on data presented in Fennell and Brown (2001). (Rat1 and rat2 results use different values for pulmonary uptake.)

or fixed as mutations and hence are less reliable measures of exposure). However, Föst et al. (1991) noted that human erythrocytes showed marked interindividual differences in the amounts of EtO bound to hemoglobin, and Yong et al. (2001) reported that levels of N-(2-hydroxyethyl)valine were approximately twofold greater in persons with a *GSTT1*-null genotype than in those with positive genotypes. Endogenous ethylene oxide (see Section 3.3.3.1) also contributes to hemoglobin adduct levels, making it more difficult to detect the impacts of low levels of exogenous EtO exposure. In addition, Walker et al. (1993) reported that hemoglobin adducts in mice and rats were lost at a greater rate than would be predicted by the erythrocyte life span.

3.3.3. Genotoxicity

Since the first report of EtO induction of sex-linked recessive lethals in Drosophila (Rapoport, 1948), numerous papers have been published on the positive genotoxic activity in biological systems, spanning the whole range of assay systems, from bacteriophage to higher plants and animals. Figure 3-3 shows the 203 test entries in the EPA Genetic Activity Profile database in 2001. 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 (from in vitro and/or in vivo exposures), EtO-induced effects include unscheduled DNA synthesis, gene mutations, sister chromatid exchanges (SCEs), micronuclei, and chromosomal aberrations. Genotoxicity, in particular increased levels of SCEs and chromosomal aberrations, has also been observed in blood cells of workers occupationally exposed to EtO. Several publications contain details of earlier genetic toxicity studies (e.g., IARC, 2008b; Kolman et al., 2002; Thier and Bolt, 2000; Natarajan et al., 1995; Preston et al., 1995; IARC, 1994b; Dellarco et al., 1990; Ehrenberg and Hussain, 1981). This review briefly summarizes the evidence of the genotoxic potential of EtO, focusing primarily on recently published studies that provide information on the mode of action of EtO (see Appendix C for more details from some individual studies).

3.3.3.1. *DNA Adducts*

EtO is a direct-acting S_N2 (substitution-nucleophilic-bimolecular)-type monofunctional alkylating agent that forms adducts with cellular macromolecules such as proteins (e.g., hemoglobin, see Section 3.3.2) and DNA (Pauwels and Veulemans, 1998). Alkylating agents may produce a variety of different DNA alkylation products (Beranek, 1990) in varying proportions, depending primarily on the electrophilic properties of the agent. Reactivity of an alkylating agent is estimated by its Swain-Scott substrate constant (*s*-value), which ranges from 0 to 1, and EtO has a high *s*-value of 0.96 (Beranek, 1990; Golberg, 1986; Warwick, 1963). Acting by the S_N2 mechanism and having a high substrate constant both favor alkylation at the N7 position of guanine in the DNA (Walker et al., 1990). The predominant DNA adduct formed by EtO and other S_N2-type alkylating agents is N7-(2-hydroxyethyl)guanine (N7-HEG). After in vitro treatment of DNA with EtO, Segerbäck (1990) identified three adducts, N7-HEG, N3-hydroxyethyladenine, and O6- hydroxyethylguanine (O^6-HEG), in the ratios 200:8.8:1; two other peaks, suspected of representing other adenine adducts, were also observed at levels well below that of N7-HEG.

Ethylene, an endogenous precursor of EtO, is produced during normal physiological processes. Such processes reportedly include oxidation of methionine and hemoglobin, lipid

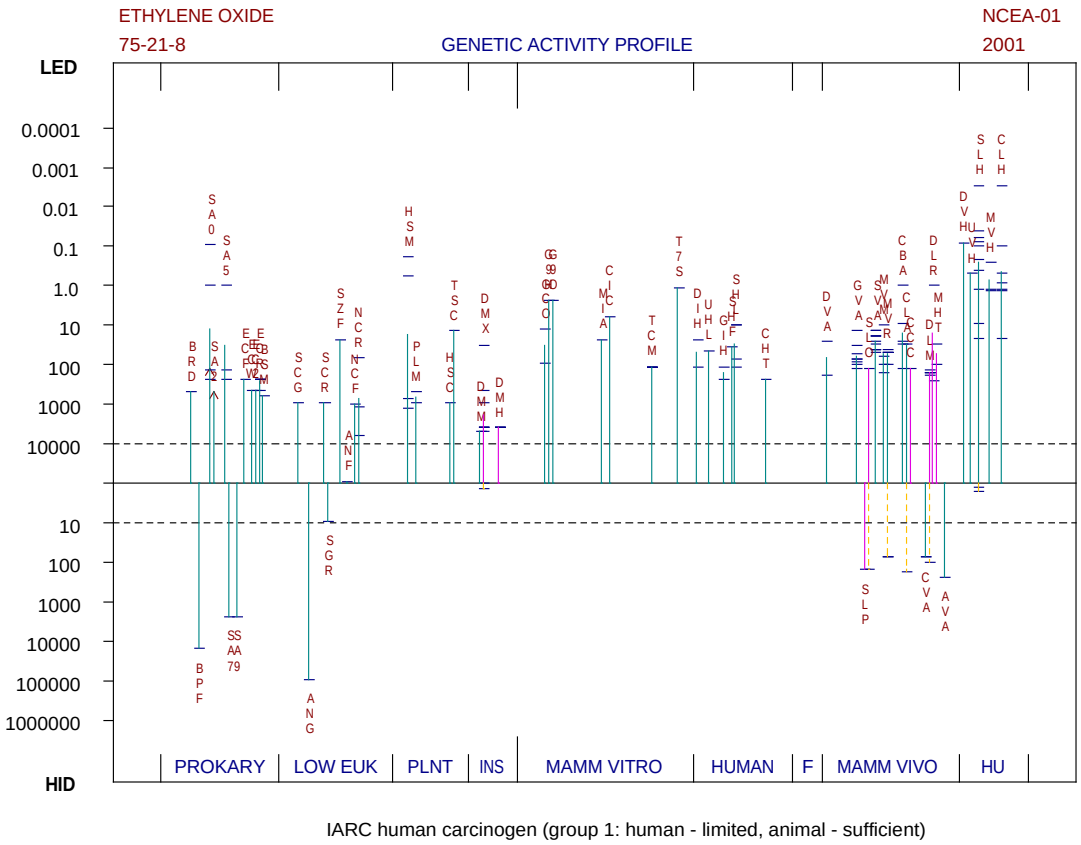

Figure 3-3. Display of 203 data sets, including bacteria, fungi, plants, insects, and mammals (in vitro and in vivo), measuring the full range of genotoxic endpoints. (This is an updated version of the figure in IARC, 1994b)

See Appendix B for list of references.

peroxidation of fatty acids, and metabolism of intestinal bacteria (reviewed in Thier and Bolt, 2000; IARC, 1994a). EtO is then endogenously produced through the cytochrome P450-mediated conversion of ethylene (Törnqvist, 1996). This endogenous production of EtO contributes significantly to background levels of DNA adducts, making it difficult to detect the impacts of low levels of exogenous EtO exposure on DNA adduct levels. For example, in DNA extracted from the lymphocytes of unexposed individuals, mean background levels of N7-HEG ranged from 2 to 8.5 pmol/mg DNA (Bolt, 1996). Using sensitive detection techniques and an approach designed to separately quantify both endogenous N7-HEG adducts and "exogenous" N7-HEG adducts induced by EtO treatment in rats, Marsden et al. (2009) reported increases in exogenous adducts in DNA of spleen and liver consistent with a linear dose-response relationship ($p < 0.05$), down to the lowest dose administered (0.0001 mg/kg injected i.p. daily

for 3 days). Note that the whole range of doses studied by Marsden et al. (2009) lies well below the dose corresponding to the lowest LOAEL from an EtO cancer bioassay (see Section C.7 of Appendix C). Marsden et al. (2009) also observed increases in endogenous N7-HEG adduct formation at the two highest doses (0.05 and 0.1 mg/kg), suggesting that, in addition to direct adduct formation via alkylation, EtO can induce N7-HEG adduct production indirectly. (Marsden et al., 2009) hypothesized that this indirect adduct formation by EtO results from the induction of ethylene generation under conditions of oxidative stress.

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. (1992a) Walker et al. (1992a) measured N7-HEG adducts 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. Although Walker et al. (1992a) suggested that N7-HEG adducts are likely to be removed by depurination forming apurinic/apyrimidinic (AP) sites in DNA, a later study from the same group showed that EtO-induced DNA damage is repaired without accumulation of AP sites or involving base excision repair (Rusyn et al., 2005). Rats exposed to high doses of EtO (300 ppm) by inhalation showed steady-state levels of O^6-HEG adducts that are ~250–300 times lower than the N7-HEG levels (Walker et al., 1992a). Even though low levels of O^6-HEG adducts were detected, they are more mutagenic in nature and may contribute to the tumors observed in target organs.

Two studies provide evidence of N7-HEG DNA adduct formation in human populations occupationally exposed to EtO, one reporting a modest increase in white blood cells (van Delft et al., 1994) and the other a four- to fivefold increase in granulocytes (Yong et al., 2007) compared to unexposed controls. However, these differences were not statistically significant due to high interindividual variation in adduct levels.

3.3.3.2. *Point Mutations*

EtO has consistently yielded positive results in in vitro mutation assays from bacteriophage, bacteria, fungi, yeast, insects, plants, and mammalian cell cultures (including human cells). For example, EtO induces single base pair deletions and base substitutions in the *HPRT* gene in human diploid fibroblasts (Kolman and Chovanec, 2000; Lambert et al., 1994; Bastlová et al., 1993) in vitro. The results of in vivo studies on the mutagenicity of EtO have also been consistently positive following ingestion, inhalation, or injection (e.g., Tates et al., 1999). Increases in the frequency of gene mutations in T-lymphocytes (*Hprt* locus) (Walker et

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

In a study of mammary gland carcinomas in EtO-exposed $B6C3F_1$ mice from the 1987 NTP bioassay (NTP, 1987) and 19 mammary gland carcinomas from concurrent controls in the 1987 NTP EtO bioassay and a 1986 NTP benzene bioassay, Houle et al. (2006) measured mutation frequencies in exons 5−8 of the *p53* tumor suppressor gene and in codon 61 of the *Hras* oncogene. Mutation frequencies in the mammary carcinomas of EtO-exposed mice were only slightly increased over frequencies in spontaneous mammary carcinomas (33% of the carcinomas in the EtO-exposed mice had *Hras* mutations versus 26% of spontaneous tumors; 67% of the carcinomas in the EtO-exposed mice had *p53* mutations versus 58% of spontaneous tumors); however, the EtO-induced tumors exhibited a distinct shift in the mutational spectra of the *p53* and *Hras* genes and more commonly displayed concurrent mutations of the two genes (Houle et al., 2006). Furthermore, Houle et al. (2006) detected about sixfold higher levels of p53 protein expression in the mammary carcinomas of EtO-exposed mice than in spontaneous mammary carcinomas, and there was an apparent dose-response relationship between EtO exposure level and both p53 protein expression and *p53* gene mutation (three of the seven tumors in the 50-ppm exposure group and all five tumors in the 100-ppm group had increased protein expression; also, three *p53* gene mutations were found in the seven tumors in the 50-ppm exposure group and nine were found in the five tumors in the 100-ppm group). Some of the same investigators conducted a similar study of *Kras* mutations in lung, Harderian gland, and uterine tumors (Hong et al., 2007). Substantial increases were observed in *Kras* mutation frequencies in the tumors from the EtO-exposed mice. *Kras* mutations were reported in 100% of the lung tumors from EtO-exposed mice versus 25% of spontaneous lung tumors (108 NTP control animal tumors, including 8 from the EtO bioassay), in 86% of Harderian gland tumors from EtO-exposed mice versus 7% of spontaneous Harderian gland tumors (27 NTP control animal tumors, including 2 from the EtO bioassay), and in 83% of uterine tumors from EtO-exposed mice (there were no uterine tumors in control mice in the 1986 NTP bioassay and none were examined from other control animals). Furthermore, a specific *Kras* mutation, a G → T transversion in codon 12, was nearly universal in lung tumors from EtO-exposed mice

(21/23) but rare in lung tumors from control animals (1/108). Other specific mutations were also predominant in the Harderian gland and uterine tumors, but too few *Kras* mutations were available in spontaneous Harderian gland tumors, and no spontaneous uterine tumors were examined; thus, meaningful comparisons could not be made for these sites. Overall, these data strongly suggest that EtO-induced mutations in oncogenes and tumor-supressor genes play a role in EtO-induced carcinogenesis in multiple tissues.

Only a few studies have investigated gene mutations in people occupationally exposed to EtO. In one study, *HPRT* mutant frequency in peripheral blood lymphocytes was measured in a group of 9 EtO-exposed hospital workers, a group of 15 EtO-exposed factory workers, and their respective controls (Tates et al., 1991). EtO exposure scenarios suggest higher exposures in the factory workers, and this is supported by the measurement of higher hemoglobin adduct levels in those workers. *HPRT* mutant frequencies were 55% increased in the hospital workers, but the increase was not statistically significant. In the factory workers, a statistically significant increase of 60% was reported. 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 3-6) 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.

Table 3-6. 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]	(Högstedt 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)

Table 3-6. 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	
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)
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 and de Jong, 1985)

Table 3-6. Cytogenetic effects in humans (continued)

[a]1 ppm = 1.83 mg ethylene oxide/m^3.
[b]Calculated by linear extrapolation.
[c]TWA (8-hr).
[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

3.3.3.3. *Chromosomal Effects*

As discussed by Preston (1999) in an extensive review of the cytogenetic effects of EtO, 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. 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. The events measured include all types of chromosomal aberrations, micronuclei, SCE, and numerical chromosomal changes. 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.

In in vitro assays, EtO has consistently tested positive in studies for multiple types of chromosomal effects, including DNA strand breaks, SCEs, micronuclei, and chromosomal aberrations (e.g., see Table 11 of IARC, 2008a). Of note, Adám et al. (2005) measured the sensitivity of different human cell types to EtO-induced DNA damage using the comet assay, which measures direct strand breaks and/or DNA damage converted to strand breaks during alkaline treatment. Adám et al. (2005) reported dose-dependent increases in DNA damage in the concentration range 0–100 μM in each of the cell types examined with no notable cytotoxicity. At the lowest concentration reported (20 μM), significant increases in DNA damage were observed in lymphoblasts, lymphocytes, and breast epithelial cells, but not in keratinocytes or cervical epithelial cells, suggesting that breast epithelial cells may have increased sensitivity to EtO-induced genotoxicity compared to other nonlymphohematopoietic cell types. In addition, Godderis et al. (2006) investigated the effects of genetic polymorphisms on DNA damage induced by EtO in peripheral blood lymphocytes of 20 nonsmoking university students. No significant increases in micronuclei were observed following EtO treatment; however, dose-related increases in DNA strand breaks were seen in the comet assay. GST polymorphisms did not have a significant impact on the EtO-induced effects; however, significant increases in DNA strand breaks were associated with low-activity alleles of two DNA repair enzymes compared to wild-type alleles.

In vivo, several inhalation studies in laboratory animals have demonstrated that EtO exposure levels in the range of those used in the rodent bioassays induce SCEs (see Table 11 of

IARC, 2008a); however, evidence for micronuclei and chromosomal aberrations from these same exposure levels is less consistent. In particular, studies by van Sittert et al. (2000) and Lorenti Garcia et al. (2001) observed increases in micronuclei and chromosomal aberrations in splenic lymphocytes of rats exposed to 50, 100, or 200 ppm EtO for 6 hours/day, 5 days/week, for 4 weeks compared to levels from control rats, but the increases were not statistically significant. IARC (2008a) noted, however, that "strong conclusions cannot be drawn" from these two studies because the cytogenetic analyses "were initiated 5 days after the final day of exposure, a suboptimal time, and the power of the (FISH) studies were limited by analysis of only a single chromosome and the small numbers of rats per group examined," which was 3 per exposure group in both of the studies, although numerous cells/rat were examined. Moreover, a recent study by Donner et al. (2010) showed clear, statistically significant increases in chromosomal aberrations with longer durations of exposure (≥12 weeks) to the concentration levels used in the rodent bioassays.

In humans, various studies of occupationally exposed workers have reported SCEs and other chromosomal effects associated with EtO exposure, including micronuclei and chromosomal aberrations. The genotoxicity of EtO was demonstrated in humans as early as 1979. Table 3-6 summarizes the cytogenetic effects of EtO on human exposures (see also Appendix C for more details on some of the studies).

As illustrated in Table 3-6, numerous studies observed increased SCEs in occupationally exposed workers, especially for workers with the highest exposures (e.g., Major et al., 1996; Sarto et al., 1991; Tates et al., 1991; Sarto et al., 1987). Several studies of occupationally exposed workers have also reported increased micronucleus formation in lymphocytes (Ribeiro et al., 1994; Tates et al., 1991), in nasal mucosal cells (Sarto et al., 1990), and in bone marrow cells (Högstedt et al., 1983), although this endpoint seems to be less sensitive than SCEs. An association between increased micronucleus frequency and cancer risk has been reported in at least one large prospective general population study (Bonassi et al., 2007). In addition, chromosomal aberrations have been reported in multiple studies of workers occupationally exposed to EtO (Ribeiro et al., 1994; Tates et al., 1991; Sarto et al., 1987). Chromosomal aberrations have been linked to an increased risk of cancer in several large prospective general population studies (e.g., Boffetta et al., 2007; Rossner et al., 2005; Hagmar et al., 2004; Liou et al., 1999).

3.3.3.4. *Summary*

The available data from in vitro studies, laboratory animal models, and epidemiological studies establish that EtO is a mutagenic and genotoxic agent that causes a variety of types of genetic damage.

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 (see Table A-5 in Appendix A), in particular lymphohematopoietic and breast cancers. Target tissues for EtO carcinogenicity in laboratory animals are varied, and the cancers are not clearly attributable to any specific type of genetic alteration. Although the precise mechanisms by which the multisite carcinogenicity in mice, rats, and humans occurs are unknown, EtO is clearly a mutagenic and genotoxic agent, as discussed in Section 3.3.3, and mutagenicity and genotoxicity are well established as playing a key role in 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 N7-HEG, although other adducts, such as N3-hydroxyethyladenine and O^6-HEG, have also been observed, in much lesser amounts (Segerbäck, 1990). In addition to direct DNA adduct formation via alkylation, Marsden et al. (2009) observed an indirect effect of EtO exposure on endogenous N7-HEG adduct formation and hypothesized that EtO could also indirectly cause adduct formation via oxidative stress (see also Section 3.3.3.1 and Appendix C). The various adducts are processed by different repair pathways, and the subsequent genotoxic responses elicited by unrepaired DNA adducts are dependent on a wide range of variables. The specific adduct(s) responsible for EtO-induced genotoxicity and the mechanism(s) by which this adduct(s) induces the genotoxic damage are unknown.

It had been postulated that the predominant EtO-DNA adduct, N7-HEG, although unlikely to be directly promutagenic, could be subject to depurination, resulting in an apurinic site which could be vulnerable to miscoding during cell replication (e.g., Walker and Skopek,

1993). However, in a study designed to test this hypothesis, Rusyn et al. (2005) failed to detect an accumulation of abasic sites in brain, spleen, and liver tissues of rats exposed to EtO. Rusyn et al. (2005) conclude that the accumulation of abasic sites is unlikely to be a primary mechanism for EtO mutagenicity, although they note that it is also possible that their assay was not sufficiently sensitive to detect small increases in abasic sites or that abasic sites are only mutagenic under conditions of rapid cell turnover, when cell replication may occur before repair of the abasic site (the tissues examined in their study were relatively quiescent). Another potential mechanism for EtO-induced mutagenicity is the direct mutagenicity of the promutagenic adducts such as O^6-HEG, although these adducts are generally considered to occur at levels too low to explain all of the observed mutagenicity (IARC, 2008a). In an in vitro study, Tompkins et al. (2009) exposed plasmid DNA to a range of EtO concentrations in water and reported that only the N7-HEG adduct was detectable after exposure to EtO concentrations up to 2,000 μM; at higher EtO concentrations (≥10 mM), N1-hydroxyethyladenine and O^6-HEG adducts were also quantifiable but at much lower levels than the N7-HEG adducts. Tompkins et al. (2009) then examined the mutagenicity of these adducts in a *supF* forward mutation assay and reported that the relative mutation frequencies were significantly elevated only for plasmids exposed to these higher EtO concentrations (see Appendix C, Sections C.1.2 and C.2.2, for a more detailed discussion of this study).

The events involved in the formation of chromosomal damage by EtO are similarly unknown. 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 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, the ends of the breaks are frequently modified by addition or deletion of nucleotides. The lack of accumulation of abasic sites observed in the Rusyn et al. (2005) study discussed above argues against a mechanism involving abasic sites as hot spots for strand breaks, although it is possible that abasic sites accumulate more readily in replicating lymphocytes, which were not examined in the study of Rusyn et al. (2005). Another postulated mechanism for EtO-induced strand breaks is via the formation of hydroxyethyl

adducts on the phosphate backbone of the DNA, but this mechanism requires further study (IARC, 2008a).

Lymphohematopoietic malignancies, like all other cancers, are considered 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 some hematopoietic cancers, there is evidence that mutations in *p53* or *NRAS* are involved in certain types of leukemia (U.S. EPA, 1997). It should also be noted that therapy-related leukemias exhibiting reciprocal translocations are generally only 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 translocations (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 M0 type (minimally differentiated acute myeloblastic leukemia) of acute myeloid leukemia (AML), and Harada et al. (2003) identified *AML1* point mutations in cases of radiation-associated and therapy-related myelodysplastic syndrome (MDS)/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. Zharlyganova et al. (2008) identified *AML1* mutations in 7 of 18 radiation-exposed MDS/AML patients but in none of 13 unexposed MDS/AML cases. Other point mutations have also been identified in therapy-related MDS/AML patients, including *p53* gene mutations after exposure to alkylating agents (Christiansen et al., 2001) and mutations in *RAS* and other genes in the receptor tyrosine kinase signal transduction pathway (Christiansen et al., 2005). Several models have been developed to integrate these various types of genetic alterations. One recent model suggests that the pathogenesis of MDS/AML can be subdivided into at least eight genetic pathways that have different etiologies and different biologic characteristics (Pedersen-Bjergaard et al., 2006).

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 relationship 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 proposed that EtO must be responsible for two nearly simultaneous DNA adducts, yielding a dose-squared (quadratic) 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, it is not clear that acute leukemia is the lymphohematopoietic cancer subtype associated with EtO exposure; in the large NIOSH study, increases in lymphohematopoietic cancer risk were driven by increases in lymphoid cancer subtypes. Furthermore, even 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). Moreover, 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. Thus, broader mode-of-action considerations were not regarded as supportive of the hypothesis that the exposure-response relationship is purely quadratic.

Breast cancer is similarly considered to be a consequence of an accumulation of genetic and epigenetic changes involving multiple genes and chromosomal alterations (Ingvarsson, 1999). Again, the precise mechanisms by which EtO induces breast cancer are unknown. As discussed in Section 3.3.3.2, in a study of mammary gland carcinomas in EtO-exposed mice, Houle et al. (2006) noted that the EtO-induced tumors exhibited a distinct shift in the mutational spectra of the *p53* and *Hras* genes and more commonly displayed concurrent mutations of the two genes. The comet assay results of Adám et al. (2005) suggest that human breast epithelial cells may have increased sensitivity to EtO-induced genotoxicity compared to other nonlymphohematopoietic cell types (see Section 3.3.3.3); however, the basis for any increased sensitivity of breast epithelial cells is similarly unknown.

In summary, EtO induces a variety of types of genetic damage. It directly interacts with DNA, resulting in DNA adducts, gene mutations, and chromosome damage. Depending on a number of variables, EtO-induced DNA adducts (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 *Nras* are also involved in some 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 provides support for a mutagenic mode of action.

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 chromosomal alterations. 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 3-2). For example, Walker et al. (1992b) and Walker et al. (1992a) 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 3.3.3). 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. Furthermore, in a study of *p53* (tumor supressor gene) and *Hras* (oncogene) mutations in mammary gland carcinomas of EtO-exposed and control mice, Houle et al. (2006) noted that the EtO-induced tumors exhibited a distinct shift in the mutational spectra of the *p53* and *Hras* genes and more commonly displayed concurrent mutations of the two genes, and in a similar study of *Kras* (oncogene) mutations in lung, Harderian gland, and uterine tumors, substantial increases were observed in *Kras* mutation frequencies in the tumors from the EtO-exposed mice (Hong et al., 2007).

Several inhalation studies in laboratory animals have demonstrated that EtO exposure levels in the range of those used in the rodent bioassays induce SCEs. Evidence for micronuclei and chromosomal aberrations from these same exposure levels has been less consistent;

however, IARC (2008a) has noted analytical limitations with some of these analyses (see Section 3.3.3.3). Moreover, a recent study by Donner et al. (2010) showed clear, statistically significant increases in chromosomal aberrations with exposure durations of ≥12 weeks to the concentration levels used in the rodent 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., 1992b) , 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, there are no compelling 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., van Sittert et al., 1993; Schulte et al., 1992; see Section 3.3.2), demonstrating the ability of EtO to bind covalently in systemic human cells, as it does in rodent cells. DNA adducts in EtO-exposed humans have not been well studied, and the evidence of increased DNA adducts is limited.

In addition, EtO has yielded positive results in in vitro mutagenicity studies of human cells (see Figure 3-3). Although the studies of point mutations in EtO-exposed humans are few and insensitive and the evidence for mutations is limited, there is clear evidence from a number of human studies that EtO causes chromosomal aberrations, SCEs, and micronucleus formation in peripheral blood lymphocytes (see Section 3.3.3.3 and Table 3-6). 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 (Högstedt 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 to 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 should be applied, in accordance with the *Supplemental Guidance* (see Section 4.4).

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-induced carcinogenicity.

3.5. HAZARD CHARACTERIZATION

3.5.1. Characterization of Cancer Hazard

In studies of humans there is substantial evidence that EtO exposure is causally associated with lymphohematopoietic cancer, but the evidence is not strong enough to be conclusive. There is also evidence that EtO exposure is causally associated with breast cancer, but the database for breast cancer is more limited. Of the eight relevant[6] Hill "criteria" (or considerations) for causality (Hill, 1965), *temporality*, *coherence*, *biological plausibility* and *analogy* are readily satisfied, and the other four criteria (*specificity, consistency, biological gradient*, and *strength of association*) are satisfied to varying degrees, as discussed below.

[6]The ninth consideration is experimental evidence, which is seldom available for human populations and is not available in the case of human exposures to EtO.

Temporality, the sole necessary criterion, is satisfied because the subjects of all the epidemiology studies of EtO were workers who were exposed to EtO before the cancers of interest were observed, i.e., exposure preceded the development of the disease.

The related criteria of *coherence*, *biological plausibility* and *analogy* are fulfilled by the well-established knowledge that EtO is mutagenic and genotoxic, which are common mechanistic features of many carcinogens; that EtO is carcinogenic in rodents, with lymphohematopoietic cancers being observed in both rats and mice and mammary carcinomas being observed in female mice; and that EtO is an epoxide and epoxides are capable of directly interacting with DNA and are the active metabolites of many carcinogens.

There is some *specificity* with respect to the lymphohematopoietic system. Most of the studies focus on examining risks associated with subcategories of the lymphohematopoietic system. These cancers include leukemia, Hodgkin lymphoma, NHL, reticulosarcoma, and myeloma. (Note that, with the exception of the Steenland et al. (2004) study, which includes lymphocytic leukemia in a lymphoid cancer category, the studies do not subcategorize leukemia into its distinct myeloid and lymphocytic subtypes.) In most of the studies, an enhanced risk of cancer of the lymphohematopoietic system is evident, and in some studies, it is statistically significant. There also appears to be *specificity* across the epidemiological database for an increased risk of breast cancer. It should be noted, however, that the *specificity* criterion is not expected to be strictly satisfied by agents, such as EtO, that are widely distributed in all tissues and are direct-acting chemicals.

As just alluded to, there is evidence of *consistency* between studies with respect to cancer of the lymphohematopoietic system as a whole. Most of the available epidemiologic studies of EtO exposure have reported elevated risks of lymphohematopoietic cancer, and the studies that do not report a significant lymphohematopoietic cancer effect have major limitations, such as small numbers of cases (from small study size and/or insufficient follow-up time), inadequate exposure information, and/or reliance on external analyses (see Table 3-1 and Table A-5 in Appendix A). Overall, about 9 of 11 studies (including only the last follow-up of independent cohorts) with adequate information to determine RR estimates reported an increased risk of lymphohematopoietic cancers or a subgroup thereof, although not all were statistically significant, possibly due to the limitations noted above (see Table 3-1 and Table A-5 in Appendix A). The large, high-quality NIOSH study shows statistically significant exposure-response trends for lymphoid cancers and all lymphohematopoietic cancers (Steenland et al., 2004; see Sections D.3 and D.4 of Appendix D for results for both sexes combined). Four other studies reported statistically significant increases in risk (Swaen et al., 1996; Benson and Teta, 1993; Bisanti et al., 1993; Hogstedt, 1988; Hogstedt et al., 1986), although EtO exposures

were reportedly low in the Benson and Teta (1993) study and the increased risks may be due to other chemical exposures. Nonsignificant increases in lymphohematopoietic cancer risk were observed in four other studies, based on small numbers of cases (Coggon et al., 2004; Olsen et al., 1997; Hagmar et al., 1995; Norman et al., 1995 [with only 1 case]; Hagmar et al., 1991). Only 2 of the 11 studies showed no evidence of an increase in lymphohematopoietic cancer risk (Swaen et al., 2009; Kiesselbach et al., 1990).

Regarding *consistency* in the breast cancer studies, the large, high-quality NIOSH study shows statistically significant increased risks for both breast cancer mortality (n = 103 deaths; (Steenland et al., 2004)) and breast cancer incidence (n = 319 cases; (Steenland et al., 2003)). Two other studies suggest an increased risk of breast cancer despite their small size ((Norman et al., 1995), n = 12 cases; (Kardos et al., 2003), n = 3 deaths). No elevated risks were seen in the only other two studies reporting breast cancer results; however these studies had few cases, owing to their small size and/or inadequate follow-up time ((Hagmar et al., 1991), n = 5 cases; (Coggon et al., 2004), n = 11 deaths) (see Table 3-2 and Table A-5 in Appendix A).

There is also some evidence of dose-response relationships (*biological gradient*). In the large, high-quality NIOSH study, a statistically significant positive trend was observed in the risk of lymphohematopoietic cancers with increasing (log) cumulative exposure to EtO, although results for this model were reported only for males (Steenland et al., 2004) [the sex difference is not statistically significant, however, and the trend for both sexes combined is also statistically significant (see Tables D-3e and D-4e in Appendix D)]. For only two other cohorts were results for exposure-response analyses reported, probably because most cohorts had too few cases and/or lacked adequate exposure information. In the Swaen et al. (2009) study of the UCC cohort, no statistically significant trends were observed for leukemia or lymphoid cancer using a Cox proportional hazards model with cumulative exposure, a model which notably did not yield statistically significant trends in the NIOSH study, either. In the small study of Hagmar et al. (1995), an SIR for leukemia of 7.14 was reported for subjects with at least 0.14 ppm × years of cumulative exposure and 10 years latency, but this result was based on only two cases and was not statistically significant. For breast cancer, exposure-response analyses were reported only for the NIOSH cohort, again presumably because most cohorts had too few cases and/or lacked adequate exposure information. These analyses yielded clear, statistically significant trends for both breast cancer mortality (Steenland et al., 2004) and breast cancer incidence (Steenland et al., 2003) for a variety of models.

Whereas most of the considerations are largely satisfied, as discussed above, there is little *strength* in the associations, as reflected by the modest magnitude of most of the RR estimates. For example, in the large NIOSH study, the RR estimate for lymphoid cancer mortality in the

highest exposure quartile is about 3.0 and the RR estimate for breast cancer incidence in the highest exposure quintile in the subcohort with interviews is on the order of 1.9. While large RR estimates increase the confidence that an observed association is not likely due to chance, bias, or confounding, modest RR estimates, such as those observed with EtO, do not preclude a causal association (U.S. EPA, 2005a). With EtO, the modest RR estimates may, in part, reflect the relatively high background rates of these cancers, particularly of breast cancer incidence.

In addition to the Hill criteria, other factors such as *chance, bias, and confounding* are considered in analyzing the weight of epidemiological evidence. Given the consistency of the findings across studies and the exposure-response relationships observed in the largest study, none of these factors is likely to explain the associations between these cancers and EtO exposure. Coexposures to other chemicals are expected to have occurred for workers in the chemical industry cohorts but would have been much less likely in the sterilizer worker cohorts, such as the NIOSH cohort, which reported no evidence of confounding exposures to other occupational carcinogens (Steenland et al., 1991). For breast cancer in the NIOSH subcohort with interviews (Steenland et al., 2003), other risk factors for breast cancer were assessed, and statistically significant factors were included in the exposure-response models.

In conclusion, the overall epidemiological evidence for a causal association between EtO exposure and lymphohematopoietic cancer was judged to be strong but less than conclusive. For breast cancer, the existing evidence was strong, but there were few studies and, thus, overall, the epidemiological evidence was judged to be more limited.

There is inadequate evidence for other cancer types (e.g., stomach cancer and pancreatic cancer) in the epidemiology studies.

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 EtO genotoxicity and mutagenicity is unequivocal. 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 (including human cells), EtO-induced genotoxic effects include unscheduled DNA synthesis, gene mutations, SCEs, and chromosomal aberrations. The results of in vivo genotoxicity studies of EtO have also been largely positive, following ingestion, inhalation, or injection. Increases in frequencies of gene mutations have been reported

in the lung, T-lymphocytes, bone marrow, and testes of EtO-exposed mice. In particular, increases in frequencies of oncogene mutations have been observed in several tumor types from EtO-exposed mice compared to spontaneous mouse tumors of the same types. Several inhalation studies in laboratory animals have demonstrated that EtO exposure levels in the range of those used in the rodent bioassays (i.e., 10–100 ppm, 6–7 hours/day, 5 days/week) induce SCEs. Evidence for micronuclei and chromosomal aberrations from these same exposure levels in short-term studies (4 weeks or less) is less consistent, although concerns have been raised about some of the negative studies. A recent study showed clear, statistically significant increases in chromosomal aberrations with longer durations of exposure (≥12 weeks) to the concentration levels used in the rodent bioassays. The studies of point mutations in EtO-exposed humans are few and insensitive and the evidence for mutations is limited; however, there is clear evidence from a number of human studies that EtO causes chromosomal aberrations, SCEs, and micronucleus formation in peripheral blood lymphocytes, and one study has reported increased levels of micronuclei in bone marrow cells in EtO-exposed workers.

Under EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the conclusion can be made that EtO is "carcinogenic to humans." In general, the descriptor "carcinogenic to humans" is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer. This descriptor is also appropriate when there is a lesser weight of epidemiologic evidence that is strengthened by specific lines of evidence set forth in the *Guidelines*, which are satisfied for EtO. The lines of evidence supporting the characterization of "carcinogenic to humans" include the following: (1) there is strong, although less than conclusive on its own, evidence of cancer in humans associated with EtO exposure via inhalation, specifically, evidence of lymphohematopoietic cancers and female breast cancer in EtO-exposed workers; (2) there is extensive evidence of EtO-induced carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure; (3) EtO is a direct-acting alkylating agent whose mutagenic and genotoxic capabilities have been well established in a variety of experimental systems, and a mutagenic mode of carcinogenic action has been identified in animals involving the key precursor events of DNA adduct formation and subsequent DNA damage, including point mutations and chromosomal effects; and (4) there is strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage, such as chromosomal aberrations, SCEs, and micronuclei in EtO-exposed workers.

3.5.2. Susceptible Life stages and Populations

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 children 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. In the absence of data on the relative susceptibility associated with EtO exposure in early life, increased early-life susceptibility is assumed, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b), because the weight of evidence supports the conclusion of a mutagenic mode of action for EtO carcinogenicity (see Section 3.4).

Other than the occurrence of sex-specific cancers (e.g., breast cancer in human females, mammary and uterine carcinomas in female mice, and testicular peritoneal mesotheliomas in male rats; see Section 3.2), there is no clear sex difference in EtO-induced carcinogenicity. With the exception of the sex-specific cancers and the observation of malignant lymphomas in female but not male mice, there is no sex difference in EtO-induced cancer types in the rat and mouse bioassays. Cancer potency estimates for females are roughly 50% higher than those for males for both mice and rats (see Table 4-18 in Section 4.2.5). In humans, in the large NIOSH study (Steenland et al., 2004), the association between lymphoid cancers and EtO exposure was seen primarily in males, but the sex difference was not statistically significant (see Appendix D), and the SAB panel that reviewed an earlier draft of this assessment recommended that data from both sexes be combined for the derivation of quantitative risk estimates for the lymphohematopoietic cancers (SAB, 2007).

Brown et al. (1996) reported that sex differences in EtO toxicokinetics were observed in mice but not in rats; female mice had a significantly higher steady-state blood EtO concentration after 4 hours of exposure to either 100 or 330 ppm than male mice. As noted above and discussed in Section 3.3.1, EtO is metabolized primarily by hydrolysis in humans. Mertes et al. (1985) reported no sex difference in microsomal or cytosolic epoxide hydrolase activities in human liver in vitro using benzo[*a*]pyrene 4,5-oxide or *trans*-stilbene oxide, respectively, as substrates. Using EtO as a substrate, but with far fewer subjects, Fennell and Brown (2001)

reported similar values for males and females for epoxide hydrolase activity in human liver microsomes and for GSH transferase in human liver cytosolic fractions.

Because EtO is detoxified by glutathione conjugation or hydrolysis, people with genotypes conveying deficiencies in glutathione-S-transferase or epoxide hydrolase activities may be at increased risk of cancer from EtO exposure. 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. Similarly, in a study of hospital workers, Haufroid et al. (2007) reported increased urinary excretion of a glutathione conjugate of EtO, reflecting increased detoxification of EtO, associated with a nonnull GSTT1 genotype, although the increase was not statistically significant in all the regression models tested; associations were less clear for other glutathione-S-transferase or epoxide hydrolase polymorphisms.

In addition, people with DNA repair deficiencies such as xeroderma pigmentosum, Bloom's syndrome, Fanconi anemia, and ataxia telangiectasia (Gelehrter et al., 1990) are expected to be especially sensitive to the damaging effects of EtO exposure. Paz-y-Miño 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.

4. CANCER DOSE-RESPONSE ASSESSMENT FOR INHALATION EXPOSURE

This chapter presents the derivation of cancer unit risk estimates from human and rodent data. Section 4.1 discusses the derivation of unit risk estimates for lymphohematopoietic cancers, breast cancer, and total cancer from human data, as well as sources of uncertainty in these estimates. Section 4.2 presents the derivation of unit risk estimates from rodent data. Section 4.3 summarizes the unit risk estimates derived from the different data sets. Section 4.4 discusses adjustments for assumed increased early-life susceptibility, based on recommendations from EPA's *Supplemental Guidance* (U.S. EPA, 2005b), because the weight of evidence supports the conclusion of a mutagenic mode of action for EtO carcinogenicity (see Section 3.4). Section 4.5 presents conclusions about the unit risk estimates. Section 4.6 compares the unit risk estimates derived in this EPA assessment to those derived in other assessments. Finally, Section 4.7 provides risk estimates derived for some general occupational exposure scenarios.

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 (most recent update by Steenland et al., 2004; Steenland et al., 2003) 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 using a comprehensive exposure assessment, (2) the cohort was large and diverse (e.g., 55% female), and (3) there was little reported exposure to chemicals other than EtO. Exposure estimates, including estimates for early exposures for which no measurements were available, were determined using a regression model that estimated exposures to each individual as a function of facility, exposure category, and time period. The regression model was based on extensive personal monitoring data from 18 facilities spanning a number of years as well as information on factors influencing exposure, such as engineering controls (Hornung et al., 1994; see also Section A.2.8 in Appendix A). When evaluated against test data, the model accounted for 85% of the variation in average EtO exposure levels. 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 follow-up results for the cohort mortality study previously discussed by Steenland et al. (1991) and Stayner et al. (1993). Positive findings in the current follow-up include increased rates of (lympho)hematopoietic cancer mortality 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 (most recent update by Swaen et al., 2009) described risks to Union Carbide workers exposed to EtO at two chemical plants in West Virginia, but this study is less useful for estimating quantitative cancer risks for a number of reasons. First, the exposure assessment is much less extensive than that used for the NIOSH cohort, with greater likelihood for exposure misclassification, especially in the earlier time periods when no measurements were available (1925–1973). Exposure estimation for the individual workers was based on a relatively crude exposure matrix which cross-classified 3 levels of exposure intensity with 4 time periods. The exposure estimates for 1974–1988 were based on measurements from air sampling at the West Virginia plants since 1976. The exposure estimates for 1957–1973 were based on measurements in a similar plant in Texas. The exposure estimates for 1940–1956 were based loosely on "rough" estimates reported for chlorohydrin-based EtO production in a Swedish facility in the 1940s. The exposure estimates for 1925–1939 were essentially guesses. Thus, for the two earliest time periods (1925–1939 and 1940–1956) at least, the exposure estimates are highly uncertain. (See Section A.2.20 of Appendix A for a more detailed discussion of the exposure assessment for the Union Carbide cohort.) This is in contrast to the NIOSH exposure assessment in which exposure estimates were based on extensive sampling data and regression modeling. In addition, the sterilization processes used by the NIOSH cohort workers were fairly constant back in time, unlike chemical production processes, which likely involved much higher and more variable exposure levels in the past. Furthermore, the Union Carbide cohort is of much smaller size and has far fewer deaths than the NIOSH cohort, it is restricted to males and so cannot be used to investigate breast cancer risk in females, and there are coexposures to other chemicals.

A third study (Hagmar et al., 1995; Hagmar et al., 1991) estimated cumulative exposures for individual workers; however, insufficient exposure-response data are presented for the derivation of unit risk estimates. Exposure-response results for specific cancers are provided only in the 1991 paper and then only for two lymphohematopoietic cancers across two categorical exposure groups.

Table 4-1 provides a summary of the judgments made in selecting the NIOSH study as the basis for the derivation of unit risk estimates. The NIOSH EtO cohort data can be obtained from the Industrywide Studies Branch of NIOSH.[7]

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

[7]Industrywide Studies Branch; Division of Surveillance, Hazard Evaluations and Field Studies: NIOSH; Centers for Disease Control and Prevention, 4676 Columbia Parkway MS R-13,Cincinnati, Ohio 45226, telephone: 513-841-4203.

Table 4-1. Considerations used in this assessment for selecting epidemiology studies for quantitative risk estimation

Consideration	Studies Selected	Comments
Availability of quantitative exposure estimates	1. Hagmar et al. (1995) and Hagmar et al. (1991) [Swedish sterilizer cohort] 2. Swaen et al. (2009) [latest follow-up of Union Carbide Corporation (UCC) cohort] 3. Steenland et al. (2004) and Steenland et al. (2003) [latest follow-up of NIOSH cohort]	These are the only 3 studies with quantitative exposure estimates, which is an essential criterion for quantitative risk estimation.
Availability of exposure-response information	1. Swaen et al. (2009) 2. Steenland et al. (2004) and Steenland et al. (2003)	Hagmar et al. (1995) and Hagmar et al. (1991) did not present sufficient exposure-response results, presumably because they had a short follow-up time and thus few cases of specific cancers (5 breast cancer cases; 6 lymphohematopoietic cancer cases).
Other factors affecting the utility of epidemiology studies for quantitative risk estimation	Steenland et al. (2004) and Steenland et al. (2003)	The NIOSH study [Steenland et al. (2004) and Steenland et al. (2003)] alone was selected for quantitative risk estimation, as it was judged to be substantially superior to the UCC study (Swaen et al., 2009) with respect to a number of key considerations [in particular, in order of importance: (1) quality of the exposure estimates, (2) cohort size, and (3) the absence of coexposures and the inclusion of women].

incidence 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.

The exposure-response models used to fit the epidemiological data are empirical "curve-fitting" models. Considerations used in the selection of the exposure-response models upon which to base the derivation of unit risk estimates included statistical fit (as reflected by *p*-values), visual fit of the models to the categorical results, and biological plausibility. When multiple models were deemed to be reasonable candidates for selection based on those considerations, AIC[8] was also considered in selecting the "preferred" model.

[8]Akaike Information Criteria. The AIC is a measure of information loss from a dose-response model that can be used to compare a specified set of models. The AIC is defined as $2p - 2\ln(L)$, where p is the number of estimated parameters included in the model and L is the maximized value of the likelihood function. Among a set of specified models, the model with the lowest AIC is the preferred model.

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 (any) 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 SMR 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

$$\text{Relative rate (RR)} = e^{\beta X}, \qquad (4\text{-}1)$$

where β represents the regression coefficient and X is the exposure (or some function of exposure, e.g., the natural log of exposure). Internal analyses were done two ways—with exposure as a categorical variable and with exposure as a continuous variable. 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.

For lymphohematopoietic cancer mortality, Steenland et al. (2004) analyzed both all lymphohematopoietic cancers combined and a subcategory of lymphohematopoietic cancers that they called "lymphoid" cancers; these included NHL, myeloma, and lymphocytic leukemia. Their exposure-response analyses focused on cumulative exposure and (natural) log cumulative exposure, with various lag periods. 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. A lag period defines an interval before death, or end of follow-up, during which any exposure is disregarded because it is not considered relevant to the outcome under investigation. For lymphohematopoietic (and lymphoid) cancer mortality, a 15-year lag provided the best fit to the data, based on the likelihood ratio test. One ppm × day was added to cumulative exposures in lagged analyses to avoid taking the log of 0. For both all lymphohematopoietic and lymphoid

cancers, Steenland et al. (2004) found stronger positive exposure-response trends in males and so presented the results for some of the regression models separately by sex. The apparent sex difference was not statistically significant (see Appendix D), however, and results for both sexes combined were subsequently obtained from Dr. Steenland (see Appendix D; Section 3 for lymphoid cancer, Section 4 for all lymphohematopoietic cancer). These results are presented in Table 4-2. For additional details and discussion of the Steenland et al. (2004) study, see Appendix A.

Table 4-2. Cox regression results for all lymphohematopoietic cancer and lymphoid cancer mortality in both sexes in the NIOSH cohort, for the models presented by Steenland et al. (2004)

Exposure variable[a]	*p* value[b]	Coefficient (SE)	ORs by category[c] (95% CI)
All lymphohematopoietic cancer[d]			
Cumulative exposure, 15-yr lag	0.40	0.00000326 (0.00000349)	
Log cumulative exposure, 15-yr lag	0.009	0.107 (0.0418)	
Categorical cumulative exposure, 15-yr lag	0.10		1.00, 2.33 (0.93–5.86), 3.46 (1.33−8.95), 3.02 (1.16–7.89), 2.96 (1.12–7.81)
Lymphoid cancer[e]			
Cumulative exposure, 15-yr lag	0.22	0.00000474 (0.00000335)	
Log cumulative exposure, 15-yr lag	0.02	0.112 (0.0486)	
Categorical cumulative exposure, 15-yr lag	0.21		1.00, 1.75 (0.59–5.25), 3.15 (1.04−9.49), 2.44 (0.80–7.50), 3.00 (1.02–8.45)

[a]Cumulative exposure is in ppm × days.
[b]*P*-values from likelihood ratio test.
[c]Exposure categories are 0, >0–1,199, 1,200–3,679, 3,680–13,499, ≥13,500 ppm × days.
[d]9th revision ICD codes 200–208; results based on 74 cases.
[e]NHL, myeloma, and lymphocytic leukemia (9th revision ICD codes 200, 202, 203, 204); results based on 53 cases.
Source: Additional analyses performed by Dr. Steenland (see Sections D.3 and D.4 of Appendix D).

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

The exposure-response trends for lymphohematopoietic cancers observed by Steenland et al. (2004) appear to be driven largely by the lymphoid cancers; therefore, the primary risk analyses for lymphohematopoietic cancer are based on the lymphoid cancer results. Lymphohematopoietic cancers are a diverse group of diseases with diverse etiologies, and

myeloid and lymphoid cells develop from different progenitor cells; thus, there is stronger support for an etiologic role of EtO in the development of lymphoid cancers than in the development of the cancers in the aggregate all lymphohematopoietic cancer category. The consideration of NHL, (plasma cell) myeloma, and lymphocytic leukemia together as "lymphoid" cancers is consistent with the current World Health Organization classification of such cancers based on their derivation from B-cells, T-cells, and NK-cells rather than previous distinctions (Harris et al., 1999). Nonetheless, for comprehensiveness and for the reasons listed below, risk estimates based on the all lymphohematopoietic cancer results are presented for comparison. Judging roughly from the *p*-values, the model fits do not appear notably better for lymphoid cancers than for all lymphohematopoietic cancers (see Table 4-2, *p*-values for log cumulative exposure models), and the "lymphoid" category did not include Hodgkin lymphoma, which also exhibited evidence of exposure-response trends, although based on few cases (Steenland et al., 2004). 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" and so could not be considered for the lymphoid cancer analysis).

The results of internal exposure-response analyses of lymphoid cancer in the NIOSH cohort (Cox regression analyses, summarized in Table 4-2) were used for predicting the extra risks of lymphoid cancer mortality from continuous environmental exposure to EtO. Extra risk is defined as

$$\text{Extra risk} = (Rx - Ro)/(1 - Ro), \qquad (4\text{-}2)$$

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 (life-table analysis) that accounts for competing causes of death.[9] An inherent assumption in the Cox regression model and its application in the life-table analyses is that RR is independent of age. (An alternate assumption of increased susceptibility from early-life exposure to EtO, as recommended in EPA's *Supplemental Guidance* (U.S. EPA, 2005b) for chemicals, such as EtO [see Section 3.4], with a mutagenic mode of action, is considered in Section 4.4. This alternate assumption is the

[9]This program is an adaptation of the approach previously used by the Committee on the Biological Effects of Ionizing Radiation (BEIR, 1988). A spreadsheet illustrating the extra risk calculation for the derivation of the LEC_{01} for lymphoid cancer incidence (see Section 4.1.1.3) is presented in Appendix E.

prevailing assumption in this assessment, based on the recommendations in the *Supplemental Guidance.* Risk estimates are first developed under the assumption of age independence, however, because that is the standard approach in the absence of evidence to the contrary or of sufficient evidence of a mutagenic mode of action to invoke the divergent assumption of increased early-life susceptibility.)

U.S. age-specific all-cause mortality rates for 2004 for both sexes of all race groups combined (Arias, 2007) were used to specify the all-cause background mortality rates in the actuarial program. For the cause-specific background mortality rates for lymphoid cancers, age-specific mortality rates for the relevant subcategories of lymphohematopoietic cancer (NHL [C82-C85 of 10th revision of the International Classification of Diseases (ICD)], multiple myeloma [C88, C90], and lymphoid leukemia [C91]) for the year 2004 were obtained from the National Center for Health Statistics Data Warehouse website (http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs.htm). The risks were computed up to age 85 for continuous exposures to EtO beginning at birth.[10] 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 EtO-contaminated 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 4-2 were used to compute the 95% upper confidence limits (UCLs) for the relative rates, based on a normal approximation.

The only statistically significant Cox regression model presented by Steenland et al. (2004) for lymphoid cancer mortality in males was for log cumulative exposure with a 15-year lag (p = 0.02). This was similarly true for the analyses of lymphoid cancer using the data for both sexes (see Table 4-2). 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 inherently 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 4-1). Some consideration was thus given to the cumulative exposure model, which is typically used and which is stable at low exposures, although the fit to these data was not statistically significant (p = 0.22). However, the Cox regression model with cumulative

[10]Rates above age 85 years are not included because cause-specific disease rates are less stable for those ages. Note that 85 years is not employed here as an average lifespan but, rather, as a cutoff point for the life-table analysis, which uses actual age-specific mortality rates. The average lifespan for males and females combined in a life-table analysis truncated at age 85 years is about 75 years.

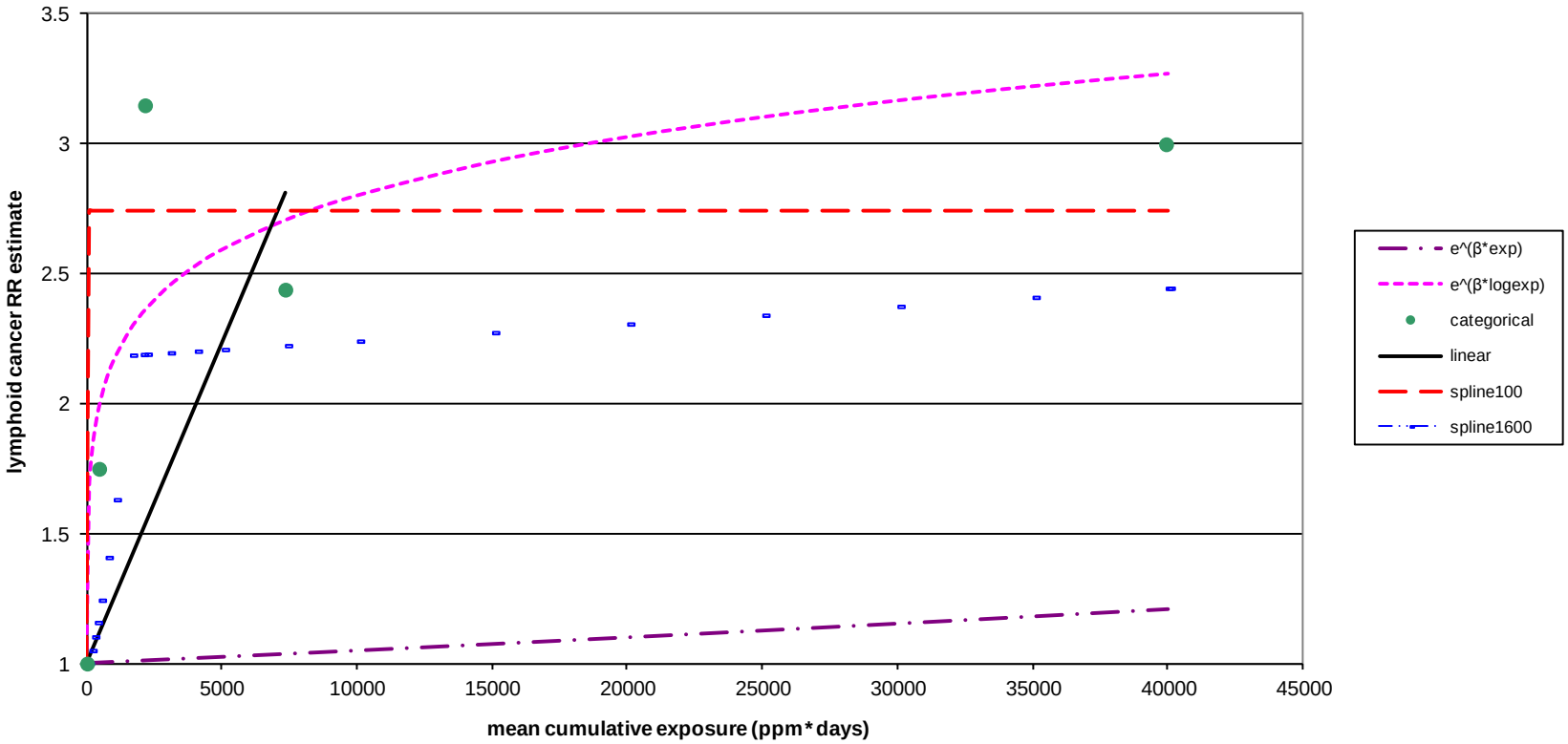

Figure 4-1. RR estimate for lymphoid cancer vs. mean exposure (with 15-year lag, unadjusted for continuous exposure).

e^(β*exp): Cox regression results for RR = $e^{(\beta \times \text{exposure})}$; e^(β*logexp): Cox regression results for RR = $e^{(\beta \times \ln(\text{exposure}))}$; categorical: Cox regression results for RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures; linear: weighted linear regression of categorical results, excluding highest exposure group (see text); spline100(1600): 2-piece log-linear spline model with knot at 100 (1,600) ppm × days (see text).

Source: Steenland reanalyses for male and female combined; see Appendix D (except for linear regression of categorical results, which was done by EPA).

exposure is inherently sublinear (i.e., risk increases gradually in the low exposure range and then with increasing steepness as exposure increases) and does not reflect the apparent supralinearity of the data demonstrated by the categorical results and the superior fit of the log cumulative exposure model; thus, this model was not considered further. (Note that all the models discussed in Chapter 4 treat exposure as a continuous variable except for the categorical models and the linear regressions of categorical data, which are specifically described as such.)

In a 2006 external review draft of this assessment (U.S. EPA, 2006a), which relied on the original published results of Steenland et al. (2004), EPA proposed that the best way to represent the exposure-response relationship in the lower exposure region, which is the region of interest for low-exposure extrapolation, was through the use of a weighted linear regression of the results from the Cox regression model with categorical cumulative exposure and a 15-year lag (for males only, as this was the significant finding in the published paper of Steenland et al., 2004). 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 (i.e., grouped) epidemiologic data and elimination of the highest exposure group(s) under certain circumstances to obtain a better fit of low-exposure data are both standard techniques used in EPA dose-response assessments (U.S. EPA, 2012, 2005a). An established methodology was employed for the weighted linear regression of the categorical epidemiologic data, as described by Rothman (1986) and used by others (e.g., van Wijngaarden and Hertz-Picciotto, 2004). However, the SAB panel that reviewed the draft assessment recommended that EPA employ models using the individual exposure data as an alternative to modeling the published grouped data. The SAB also recommended that both males and females be included in the modeling of lymphohematopoietic cancer mortality (SAB, 2007).

In response to these recommendations and in consultation with Dr. Steenland, one of the investigators from the NIOSH cohort studies, EPA determined that, using the full data set, an alternative way to address the supralinearity of the data (while avoiding the extreme low-exposure curvature obtained with the log cumulative exposure model) might be to use a two-piece log-linear spline model. Spline models have been used previously for exposure-response analyses of epidemiological data (Steenland and Deddens, 2004; Steenland et al., 2001). These models are particularly useful for exposure-response data such as the EtO lymphoid cancer data, for which RR initially increases with increasing exposure but then tends to plateau, or level off, at higher exposures. Such plateauing exposure-response relationships have been seen with other occupational carcinogens and may occur for various reasons, including the depletion of susceptible subpopulations at high exposures, mismeasurement of high exposures,

or a healthy worker survivor effect (Stayner et al., 2003). No other traditional exposure-response models for continuous data which might suitably fit the observed exposure-response pattern were apparent. Dr. Steenland was commissioned to do the spline analyses using the full data set with cumulative exposure as a continuous variable, and his findings are included in Appendix D (see Section D.3 for lymphoid cancer, Section D.4 for all lymphohematopoietic cancer). The results of the spline analyses are presented below.

For the two-piece log-linear spline modeling approach, the Cox regression model (eq 4-1) was the underlying basis for the splines which were fit to the lymphoid cancer exposure-response data.[11] Taking the log of both sides of eq 4-1, log RR is a linear function of exposure (cumulative exposure is used here), and, with the two-piece log-linear spline approach, log RR is a function of two lines which join at a single point of inflection, called a "knot". The shape of the two-piece log-linear spline model, in particular the slope in the low-exposure region, depends on the location of the knot. For this assessment, the knot was generally selected by trying different knots in increments of 1,000 ppm × days, starting at 1,000 ppm × days, and choosing the one that resulted in the largest model likelihood. In some cases, increments of 100 ppm × days were used between the increments of 1,000 ppm × days to fine-tune the knot selection. The model likelihood did not change much across the different trial knots (see Figure D-3a of Appendix D), but it did change slightly; therefore, the largest calculated likelihood was used as a basis for knot selection. For more discussion of the two-piece spline approach, see Appendix D.

Using this approach, the largest likelihood was observed with the knot at 1,600 ppm × days. However, the graphical results for the two-piece log-linear spline model with a knot at 1,600 ppm × days suggested that the model was underestimating RR in the region where the data were plateauing (see Figure 4-1).[12] Therefore, knots below 1,000 ppm × days were also evaluated in increments of 100 ppm × days, and a likelihood was observed with the knot at 100 ppm × days that exceeded the likelihood with the knot at 1,600 ppm × days, although, again, the model likelihood did not actually change much across the different trial knots. See Table 4-3 and Section D.3 of Appendix D for parameter estimates and fit statistics for the two spline models. The graphical results for the two-piece spline model with a knot at 100 ppm × days suggested that this model provided a better fit to the region where the data were plateauing (see Figure 4-1). Furthermore, the overall fit of this two-piece spline model was statistically significant ($p = 0.048$), whereas the p-value for the two-piece spline model with the knot at 1,600 ppm × days exceeded 0.05, although minimally ($p = 0.072$). Thus, for the

[11]As parameterized in Appendix D, for cumulative exposures less than the value of the knot, $RR = e^{(\beta 1 \times \text{exposure})}$; for cumulative exposures greater than the value of the knot, $RR = e^{(\beta 1 \times \text{exposure} + \beta 2 \times (\text{exposure-knot}))}$.

[12]The loglinear spline segments appear fairly linear in the plotted range; however, they are not strictly linear.

lymphoid cancer mortality data, the optimal two-piece log-linear spline model appeared to be the one with the knot at 100 ppm × days. This model provided the largest calculated likelihood, was statistically significant, and presented the best apparent graphical fit to the majority of the range of the data. However, this model yielded a very steep slope in the exposure range below the knot of 100 ppm × days (see Figure 4-1), and, as such, there was low confidence in the slope, given that it is based primarily on a relatively small number of cases in the low-exposure region. Thus, after examining the new modeling analyses, it was determined that the weighted linear regression of the categorical data still provided the best available approach for risk estimates for lymphohematopoietic cancer.[13]

Table 4-3. Exposure-response modeling results for all lymphohematopoietic cancer and lymphoid cancer mortality in both sexes in the NIOSH cohort for models not presented by Steenland et al. (2004)

Model[a]	*p* value[b]	Coefficient (SE)
All lymphohematopoietic cancer[c]		
2-piece log-linear spline (knot at 500 ppm × days)	0.02	low-exposure spline segment: B1 = 0.00201 (0.0007731)
Linear regression of categorical results, excluding highest exposure group	0.08	0.0003459 (0.0001944)
Lymphoid cancer[d]		
Optimal 2-piece log-linear spline (knot at 100 ppm × days)	0.048	low-exposure spline segment: B1 = 0.01010 (0.00493)
Alternate 2-piece log-linear spline (knot at 1,600 ppm × days)	0.07	low-exposure spline segment: B1 = 0.0004893 (0.0002554)
Linear regression of categorical results, excluding the highest exposure quartile	0.18	0.000247 (0.000185)

[a]All with cumulative exposure in ppm × days as the exposure variable and with a 15-yr lag.
[b]*p*-values from likelihood ratio test, except for linear regressions of categorical results, where Wald *p*-values are reported.
[c]9th revision ICD codes 200–208; results based on 74 cases.
[d]NHL, myeloma, and lymphocytic leukemia (9th revision ICD codes 200, 202, 203, 204); results based on 53 cases.
Source: Additional analyses performed by Dr. Steenland (see Sections D.3 and D.4 of Appendix D), except for the linear regression of the categorical results, which was performed by EPA.

[13]When this assessment was near completion, a two-piece linear spline model (with a linear model, i.e., RR = 1 + β × exposure, as the underlying basis for the spline pieces) was attempted, using the just-published approach of Langholz and Richardson (2010) to model the individual data with cumulative exposure as a continuous variable; however, this model did not alleviate the problem of the excessively steep low-exposure spline segment (see Figure D-3c in Appendix D) and was not pursued further for the lymphoid cancer data. The Langholz and Richardson (2010) approach was also employed to model the lymphoid cancer data using linear RR models with cumulative exposure and log cumulative exposure as continuous variables; however, these linear models similarly did not alleviate the problems of the corresponding log-linear RR models (see Figure D-3c in Appendix D).

For the weighted linear regression, the Cox regression results from the model with categorical cumulative exposure and a 15-year lag (see Table 4-2) was used, excluding the highest exposure group, as discussed above.[14] The weights used for the ORs were the inverses of the variances, which were calculated from the confidence intervals.[15] Mean and median exposures for the cumulative exposure groups were provided by Dr. Steenland (see Table D-3a of Appendix D).[16] 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. See Table 4-3 for the results obtained from the weighted linear regression and Figure 4-1 for a depiction of the resulting model.

As the lymphoid cancer data set is the primary data set used for the derivation of unit risk estimates for lymphohematopoietic cancers, a summary of all the models considered for modeling the lymphoid cancer exposure-response data and the judgments made about model selection is provided in Table 4-4. See Figures 4-1 and D-3c in Appendix D for visual representations of the models. See Tables 4-2 and 4-3 and Section D.3 of Appendix D for *p*-values and other fit statistics.

The linear regression of the categorical results for males and females combined and the actuarial program (life-table analysis) were 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-exposure extrapolation from epidemiological data; higher extra risk levels, such as 10%, would be an upward extrapolation for these data. Thus, 1% extra risk was selected for determination of the POD, and, consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the LEC value corresponding to that risk level was used as the POD to derive the cancer unit risk estimates.

[14]Concerns have been raised that this approach of dropping high-dose data appears arbitrary. It should be noted, however, that only the highest exposure group was omitted from the linear regression, and the exposure groupings were derived a priori by the NIOSH investigators and not by U.S. EPA in the course of its analyses.

[15]Equations for this weighted linear regression approach are presented in Rothman (1986) and summarized in Appendix F.

[16]Mean exposures for both sexes combined with a 15-year lag for the categorical exposure quartiles in Table 4-1 were 446; 2,143; 7,335; and 39,927 ppm × days. Median values were 374; 1,985; 6,755; and 26,373 ppm × days. These values are for the full cohort, not just the risk sets.

Table 4-4. Models considered for modeling the exposure-response data for lymphoid cancer mortality in both sexes in the NIOSH cohort for the derivation of unit risk estimates

Model[a]	Comments
Cox regression (log-linear) model	Inadequate overall statistical fit and poor visual fit in the low-exposure region
Cox regression model with log cumulative exposure	Good overall statistical fit but too steep in the low-exposure region
Optimal 2-piece log-linear spline (knot at 100 ppm × days)	Good overall statistical fit but too steep in the low-exposure region
Alternate 2-piece log-linear spline (knot at 1,600 ppm × days)	Nonsignificant statistical fit and too steep in the low-exposure region
linear model (RR = 1 + β × exposure)	Inadequate overall statistical fit (p = 0.13) and poor visual fit in the low-exposure region
linear model with log cumulative exposure	Good overall statistical fit (p = 0.02) but too steep in the low-exposure region
2-piece linear spline model	Good overall statistical fit (p = 0.04) but too steep in the low-exposure region
Linear regression of categorical results, excluding the highest exposure quartile	**SELECTED.** The continuous supralinear models (e.g., the log-cumulative-exposure models and the optimal 2-piece log-linear spline model) are statistically significant for lymphoid cancer mortality; however, they are too steep in the low-exposure region for the derivation of stable unit risk estimates. Thus, the linear regression model of categorical results, excluding the highest exposure quartile, was used for the derivation of unit risk estimates, despite the lack of statistical significance, as it was considered a better representation of the data in the low-exposure region. Lack of statistical significance is not critical given the low statistical power with categorical data and the statistical significance of the continuous supralinear models, which establishes the significance of the exposure-response correlation for the underlying data.

[a]All with cumulative exposure as the exposure variable, except where noted, and with a 15-yr lag.

Because EtO is DNA-reactive and has direct mutagenic activity (see Section 3.3.3), which is one of the cases cited by EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) for the use of linear low-dose extrapolation, a linear low-exposure extrapolation was performed. The EC_{01}, LEC_{01}, and inhalation unit risk estimate calculated for lymphoid cancer mortality from the linear regression of the categorical results are presented in Table 4-5 (the incidence results also presented in Table 4-5 are discussed in Section 4.1.1.3 below). The

Table 4-5. EC_{01}, LEC_{01}, and unit risk estimates for lymphoid cancer[a]

Model[c]	Mortality			Incidence[b]		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Cox regression model, log cumulative exposure, 15-yr lag	0.00441	0.000428	--[d]	0.000288	0.0000898	--[d]
Optimal low-exposure log-linear spline (knot at 100 ppm × days),[e] cumulative exposure, 15-yr lag	0.000982	0.000545	--[d]	0.000525	0.000291	--[d]
Alternate low-exposure log-linear spline (knot at 1,600 ppm × days),[f] cumulative exposure, 15-yr lag	0.0203	0.0109	--[f]	0.0108	0.00583	--[f]
Linear regression of categorical results, cumulative exposure, 15-yr lag[g]	0.0564	0.0252	0.397	0.0254	0.0114	**0.877**

[a]From lifetime continuous exposure. Unit risk = $0.01/LEC_{01}$.
[b]Incidence estimates presented here for comparison; they are derived in Section 4.1.1.3.
[c]From Dr. Steenland's analyses for males and females combined (see Section D.3 of Appendix D), Cox regression models. Note that the EC_{01} and LEC_{01} results presented here will not exactly match those presented in Appendix D because, although EPA used the regression coefficients reported by Dr. Steenland in Appendix D, the life-table analyses using 2004 all-cause mortality rates were redone to be more up-to-date and consistent with the cause-specific mortality rates; the results presented in Appendix D were based on life-table analyses using 2000 all-cause mortality rates.
[d]Unit risk estimates are not presented for these models because these models were deemed unsuitable for the derivation of risks from (low) environmental exposure levels (see text).
[e]Using regression coefficient from low-exposure segment of optimal two-piece log-linear spline model (largest likelihood) with knot at 100 ppm × days; see text and Appendix D. Each of the EC_{01} values is below the value of 0.0013 ppm roughly corresponding to the knot of 100 ppm × days [(100 ppm × days) × (10 m^3/20 m^3) × (240 d/365 d) × (365 d/yr)/70 yr = 0.0013 ppm] and, thus, appropriately in the range of the low-exposure segment.
[f]Using regression coefficient from low-exposure segment of alternate two-piece log-linear spline model (local largest likelihood) with a knot at 1,600 ppm × days. Each of the EC_{01} values is below the value of 0.021 ppm roughly corresponding to the knot of 1,600 ppm × days (see footnote d for calculation) and, thus, appropriately in the range of the low-exposure segment. Unit risk estimates were not calculated from this model because the fit was inferior to that of the optimal model (see text).
[g]Regression coefficient derived from linear regression of categorical Cox regression results from Table 4-2, as described in Section 4.1.1.2. Each of the EC_{01} values is appropriately below the value of 0.090 ppm roughly corresponding to the value of about 7,000 ppm × days (see footnote d for calculation) above which the linear regression model of the categorical results does not apply (see Figure 4-1).

resulting unit risk estimate for lymphoid cancer mortality based on the linear regression of the categorical results for both sexes using cumulative exposure with a 15-year lag is 0.397 per ppm. EC_{01} and LEC_{01} estimates from the other models considered are presented for comparison only, to illustrate the differences in model behavior at the low end of the exposure-response range. Unit risk estimates are not presented for these other models because, as discussed above, these models were deemed unsuitable for the derivation of risks from (low) environmental exposure levels. The log cumulative exposure model, with its extreme supralinearity in the lower exposure region, and the optimal two-piece log-linear spline model, with its very steep low-exposure slope, yield substantially lower EC_{01} estimates (0.00441 ppm and 0.000982 ppm, respectively). Converting the units, the resulting unit risk estimate of 0.397 per ppm from the linear regression model of the categorical results corresponds to a unit risk estimate of 2.17×10^{-4} per $\mu g/m^3$ for lymphoid cancer mortality.[17]

As discussed above, risk estimates based on the all lymphohematopoietic cancer results are also derived for comparison. The same methodology presented above for the lymphoid cancer results was used for the all lymphohematopoietic cancer risk estimates. Age-specific background mortality rates for all lymphohematopoietic cancers for the year 2004 were obtained from the NCHS Data Warehouse website (http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs.htm). The results of Dr. Steenland's reanalyses using the Cox regression models presented in the Steenland et al. (2004) paper with data for males and females combined are presented in Table 4-2. As for lymphoid cancer and for all hematopoietic cancer in males presented in the Steenland et al. (2004) paper, the only statistically significant Cox regression model was for log cumulative exposure with a 15-year lag ($p = 0.01$). The cumulative exposure model did not provide an adequate fit to the data and is not considered further here ($p = 0.35$).

Because of the problems with the supralinear log cumulative exposure model which are discussed for the lymphoid cancers above, EPA again investigated the use of a two-piece log-linear spline model to attempt to address the supralinearity of the data while avoiding the extreme low-exposure curvature obtained with the log cumulative exposure model. For the all lymphohematopoietic cancer mortality data, the largest calculated likelihood was obtained with a knot of 500 ppm × days (see Figure D-4a of Appendix D). See Table 4-3 and Section D.4 of Appendix D for parameter estimates and fit statistics for the two-piece spline model. As with the lymphoid cancer mortality results, however, this model resulted in an apparently excessively

[17]Conversion equation: 1 ppm = 1,830 $\mu g/m^3$.

steep low-exposure spline (see Figure 4-2), so, again, the linear regression model of the categorical results was used to derive the cancer unit risk estimate for this data set.[18]

For the weighted linear regression, the results from the Cox regression model with categorical cumulative exposure and a 15-year lag (see Table 4-2) were used, excluding the highest exposure group, and the approach discussed above for lymphoid cancer mortality. See Table 4-3 for the results obtained from the weighted linear regression and Figure 4-2 for a graphical presentation of the resulting linear regression model. As discussed above, this linear regression model was used to derive the unit risk estimates for all lymphohematopoietic cancer.

The EC_{01}, LEC_{01}, and inhalation unit risk estimate calculated for all lymphohematopoietic cancer mortality from the linear regression model of the categorical results are presented in Table 4-6 (the incidence results also presented in Table 4-6 are discussed in Section 4.1.1.3 below). The resulting unit risk estimate for all lymphohematopoietic cancer mortality based on the linear regression of the categorical results for both sexes using cumulative exposure with a 15-year lag is 0.680 per ppm. EC_{01} and LEC_{01} estimates from the other models considered are presented for comparison only, to illustrate the differences in model behavior at the low end of the exposure-response range. Unit risk estimates are not presented for these other models because, as discussed above, these models were deemed unsuitable for the derivation of risks from (low) environmental exposure levels. The resulting unit risk estimate for all lymphohematopoietic cancer mortality from the linear regression model of the categorical results is similar to that for lymphoid cancer mortality (70% higher; see Table 4-5). Converting the units, the resulting unit risk estimate of 0.680 per ppm corresponds to a unit risk estimate of 3.72×10^{-4} per $\mu g/m^3$ for all lymphohematopoietic cancer mortality.

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

[18]When this assessment was near completion, a two-piece linear spline model (with a linear model, i.e., RR = 1 + β × exposure, as the underlying basis for the spline pieces) was attempted, using the just-published approach of Langholz and Richardson (2010) to model the individual data with cumulative exposure as a continuous variable; however, this model did not alleviate the problem of the excessively steep low-exposure spline segment (see Figure D-4c in Appendix D) and was not pursued further for the all lymphohematopoietic cancer data. The Langholz and Richardson (2010) approach was also employed to model the all lymphohematopoietic cancer data using linear RR models with cumulative exposure and log cumulative exposure as continuous variables; however, these linear models similarly did not alleviate the problems of the corresponding log-linear RR models (see Figure D-4c in Appendix D).

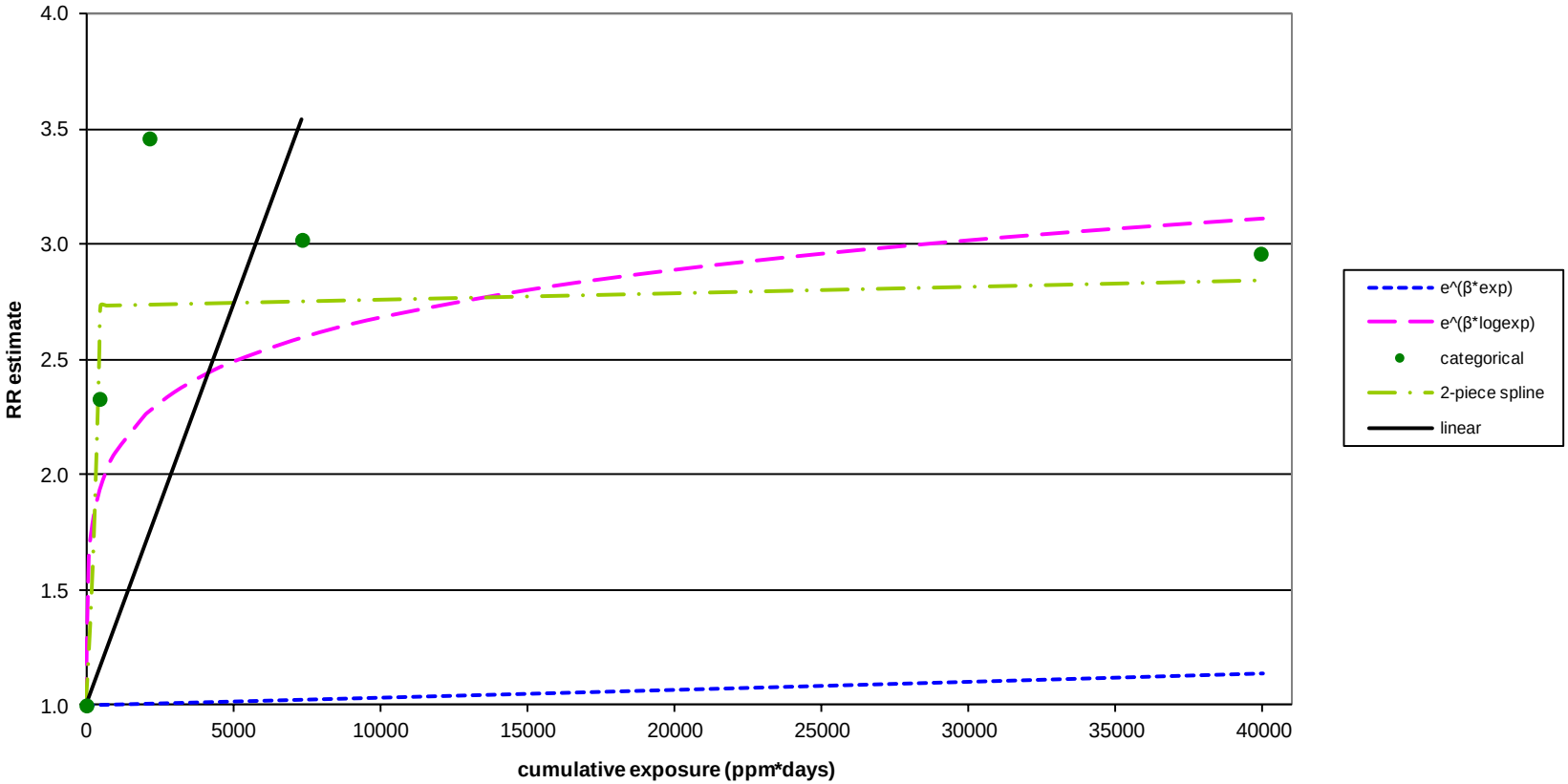

Figure 4-2. RR estimate for all lymphohematopoietic cancer vs. mean exposure (with 15-year lag, unadjusted for continuous exposure).

e^(β*exp): Cox regression results for RR = $e^{(\beta \times \text{exposure})}$; e^(β*logexp): Cox regression results for RR = $e^{(\beta \times \ln(\text{exposure}))}$; categorical: Cox regression results for RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures; linear: weighted linear regression of categorical results, excluding highest exposure group (see text); 2-piece spline: 2-piece log-linear spline model with knot at 500 ppm × days (see text)

Source: Steenland reanalyses for male and female combined; see Appendix D (except for linear regression of the categorical results, which was done by EPA).

Table 4-6. EC_{01}, LEC_{01}, and unit risk estimates for all lymphohematopoietic cancer[a]

Model[c]	Mortality			Incidence[b]		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Log cumulative exposure, 15-yr lag	0.00140	0.000245	--[d]	0.000190	0.0000753	--[d]
Low-exposure log-linear spline;[e] cumulative exposure, 15-yr lag	0.00377	0.00231	--[d]	0.00216	0.00132	--[d]
Linear regression of categorical results, cumulative exposure, 15-yr lag[f]	0.0283	0.0147	0.680	0.0144	0.00746	**1.34**[g]

[a]From lifetime continuous exposure. Unit risk = $0.01/LEC_{01}$.
[b]Incidence estimates presented here for comparison; they are derived in Section 4.1.1.3.
[c]From Dr. Steenland's analyses for males and females combined (see Appendix D), Cox regression models. Note that the EC_{01} and LEC_{01} results presented here will not exactly match those presented in Appendix D because, although EPA used the regression coefficients reported by Dr. Steenland in Appendix D, the life-table analyses using 2004 all-cause mortality rates were redone to be more up-to-date and consistent with the cause-specific mortality rates; the results presented in Appendix D were based on life-table analyses using 2000 all-cause mortality rates.
[d]Unit risk estimates are not presented for these models because these models were deemed unsuitable for the derivation of risks from (low) environmental exposure levels (see text).
[e]Using regression coefficient from low-exposure segment of two-piece log-linear spline model with knot at 500 ppm × days; see text and Appendix D. Each of the EC_{01} values is below the value of 0.0064 ppm roughly corresponding to the knot of 500 ppm × days [(500 ppm × days) × (10 m^3/20 m^3) × (240 d/365 d) × (365 d/yr)/70 yr = 0.0064 ppm] and, thus, appropriately in the range of the low-exposure segment.
[f]Regression coefficient derived from linear regression of categorical Cox regression results from Table 4-2, as described in Section 4.1.1.2. Each of the EC_{01} values is appropriately below the value of 0.064 ppm roughly corresponding to the value of about 5,000 ppm × days (see footnote d for calculation) above which the linear regression model of the categorical results does not apply (see Figure 4-2).
[g]For unit risk estimates below 1, convert to risk per ppb (e.g., 1.34 per ppm = 1.34×10^{-3} per ppb).

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 (see Section 4.1.1.2), but with age-specific lymphoid cancer incidence rates for the relevant subcategories of lymphohematopoietic cancer (NHL, myeloma, and lymphocytic

leukemia) for 2000–2004 from SEER (Ries et al., 2007); Tables XIX, XVIII, XIII: both sexes, all races) in place of the lymphoid 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 17," a registry of seventeen states, regions, and cities covering about 26% of the U.S. population.

The incidence-based calculation assumes that lymphoid 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 lymphoid cancer or that relapses and secondary lymphoid cancers provide a negligible contribution. (The latter assumption is probably sound; the former assumption is more potentially problematic. Because various lymphoid subtypes with different survival rates are included in the categorization of lymphoid cancers, if the EtO-associated relative rates of the subtypes differ and if the relative rate-weighted survival rates for the lymphoid 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 lymphoid cancer incidence.)[19] Potential concern that the incidence estimates might be overestimated would come primarily from the inclusion of multiple myeloma, because that subtype has the lowest incidence:mortality ratios (and, thus, if that subtype were driving the increased mortality observed for the lymphoid cancer grouping, then including the incidence estimates). Multiple myelomas, however, constitute only 25% of the lymphoid cancer cases in the cohort, and there is no evidence that multiple myeloma is driving the EtO-induced rates for the other subtypes, which have higher incidence:mortality ratios, might inflate the not expected to result in an overestimation of the incidence risk estimates; if anything, the incidence risks would likely be diluted with the inclusion of the multiple myeloma rates. The incidence-based calculation also relies on the fact that the lymphoid cancer incidence rates are excess in lymphoid cancer mortality.[20] Thus, using the total lymphoid cancer incidence rates is small when

[19]Sielken and Valdez-Flores (2009) reject the assumption that lymphohematopoietic cancer incidence and mortality have the same exposure-response relationship, reporting that, except at high exposure levels, the exposure-response data in the male workers in the NIOSH cohort are consistent with a decreased survival time and suggesting that this could explain the observed increases in mortality. However, they do not establish that this is what is occurring, and the mechanistic data support an exposure-related increase in incident cancers. See Appendix A.2.20 for a more detailed discussion of this issue.

[20]According to data from SEER (www.seer.cancer.gov), 25% is below the proportion of multiple myeloma deaths one would expect based on age-adjusted U.S. background mortality rates of multiple myeloma, NHL, and chronic lymphocytic leukemia, and these 3 subtypes have the same pattern for mortality rates increasing as a function of age mostly above age 50, so the comparison with lifetime background rates is reasonable. In addition, the low proportion of multiple myeloma deaths in the lymphoid cancer subgrouping cannot be attributed to an underrepresentation of blacks, who have incidence rates of multiple myeloma over twice those of whites (http://seer.cancer.gov/statfacts/html/mulmy.html), in the cohort, because blacks comprise 16% of the cohort versus 12.3% in the U.S. population.

compared with the all-cause mortality rates.[21] The resulting EC_{01} and LEC_{01} estimates for lymphoid cancer incidence from the various models examined are presented in Table 4-5. The unit risk estimate for lymphoid cancer incidence from the selected linear regression model of the categorical results is 0.877 per ppm.

The EC_{01} estimates for cancer incidence range from about 6.5% (log cumulative exposure Cox regression model) to 54% (cumulative exposure Cox regression model) of the corresponding mortality-based estimates. The difference between incidence and mortality rates cannot explain the large discrepancy in EC_{01} estimates for the log cumulative exposure model. Instead, the discrepancy probably reflects the very different results that can occur from a small shift along the dose-response curve for the log cumulative exposure model, illustrating the low-dose instability of the results from this model. The incidence unit risk estimate from the linear regression model of the categorical results is about 120% higher than (i.e., 2.2 times) the mortality-based estimate.

Overall, as discussed above, the preferred estimate for the unit risk for lymphoid cancer is the estimate of **0.877 per ppm** (4.79×10^{-4} per $\mu g/m^3$) derived, using incidence rates for the cause-specific background rates, from the weighted linear regression of the categorical results, dropping the highest exposure group.

As discussed in Section 4.1.1.2, risk estimates based on the results of Dr. Steenland's reanalyses of the all lymphohematopoietic cancer data (see Appendix D and Table 4-2) are also derived for comparison. The same methodology presented above for the lymphoid cancer incidence results was used for the all lymphohematopoietic cancer incidence risk estimates, and the same assumptions apply. Age-specific SEER incidence rates for all lymphohematopoietic cancer for the years 2000−2004 were used (Ries et al., 2007); Tables XIX, IX, XVIII, and XIII: both sexes, all races). The EC_{01} and LEC_{01} estimates for all lymphohematopoietic cancer incidence from the different all lymphohematopoietic cancer mortality models examined are presented in Table 4-6. The resulting unit risk estimate for all lymphohematopoietic cancer incidence from the linear regression of the categorical results is about 2.0-times the mortality-based estimate and about 1.5-times the lymphoid cancer incidence estimate (see Table 4-5).

[21]Sielken and Valdez-Flores (2009) suggest that the methods used by EPA to calculate incidence risk estimates in the life-table analysis are inappropriate; however, as explained in more detail in Appendix A.2.20, we disagree. For the situation where the cause-specific incidence rates are small compared to the all-cause mortality rates, as with lymphoid cancer, there is no problem, as Sielken and Valdez-Flores (2009) themselves demonstrate, and, for the situation where the cause-specific incidence rates are not negligible compared to the all-cause mortality rates, as with breast cancer, an adjustment was made in the analysis to remove those with incident cases from the population at risk, i.e., those "surviving" each interval without a diagnosis of breast cancer (see Section 4.1.2.3). See Appendix A.2.20 for a more detailed discussion of this issue.

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. In addition to the analyses presented in the Steenland et al. (2003) and Steenland et al. (2004) papers, Dr. Steenland did subsequent analyses of the breast cancer incidence and mortality data sets for EPA; these are discussed below and reported in Sections D.1 and D.2 of Appendix D, respectively.

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

Results from the Cox regression models presented by Steenland et al. (2004), with some reanalyses reported by Dr. Steenland in Appendix D (see Section D.2), are summarized in Table 4-7. These models were considered for the derivation of unit risk estimates for breast cancer mortality in females from continuous environmental exposure to EtO, applying the methodologies described in Section 4.1.1.2.

Table 4-7. Cox regression results for breast cancer mortality in females in the NIOSH cohort[a], for models presented in Steenland et al. (2004)

Exposure variable[b]	*p*-value[c]	Coefficient (SE)	ORs by category[d] (95% CI)
Cumulative exposure, 20-yr lag[e]	0.06	0.0000122 (0.00000641)	
Log cumulative exposure, 20-yr lag[f]	0.01	0.084 (0.035)	
Categorical cumulative exposure, 20-yr lag[f]	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 breast cancer (ICD-9 174,175) deaths.
[b]Cumulative exposure is in ppm × days.
[c]*p*-values reported by Steenland et al. (2004).
[d]Exposure categories are 0; >0–646; 647–2,779; 2,780–12,321; ≥12,322 ppm × days.
[e]From reanalyses in Section D.2 of Appendix D; Steenland et al. (2004) reported the Cox regression results for cumulative exposure with no lag.
[f]From Table 8 of Steenland et al. (2004).

United States age-specific all-cause mortality rates for 2000 for females of all race groups combined (Miniño et al., 2002) were used to specify the all-cause background mortality rates in

the actuarial program (life-table analysis). The National Center for Health Statistics 1997–2001 cause-specific background mortality rates for invasive breast cancers in females were obtained from a SEER report (Ries et al., 2004). 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 only statistically significant 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 4-3). The cumulative exposure model, which is typically used and which is stable at low exposures, was nearly statistically significant ($p = 0.06$ with a 20-year lag; see Section D.2 of Appendix D) in terms of the global fit to the data; however, at low exposures, the Cox regression model with cumulative exposure is sublinear and does not reflect the apparent supralinearity of the breast cancer mortality data (see Figure 4-3).

In a 2006 external review draft of this assessment (U.S. EPA, 2006a), which relied on the original published results of Steenland et al. (2004), EPA proposed that the best way to reflect the exposure-response relationship 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 Cox regression model with categorical cumulative exposure and a 20-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) in certain circumstances to obtain a better fit of low-exposure data are both standard techniques used in EPA dose-response assessments (U.S. EPA, 2005a). However, as discussed in Section 4.1.1.2 for the similarly supralinear lymphohematopoietic cancer data, the SAB panel that reviewed the draft assessment recommended that EPA employ models using the individual exposure data as an alternative to modeling the published grouped data (SAB, 2007). Consequently, it was determined that, using the full data set, an alternative way to address the supralinearity of the data (while avoiding the extreme low-exposure curvature obtained with the log cumulative exposure model) might be to use a two-piece spline model, and Dr. Steenland was commissioned to do the spline analyses using the full data set with cumulative exposure as a continuous variable. His findings are reported in Section D.2 of Appendix D, and the results for the breast cancer mortality analyses are summarized below.

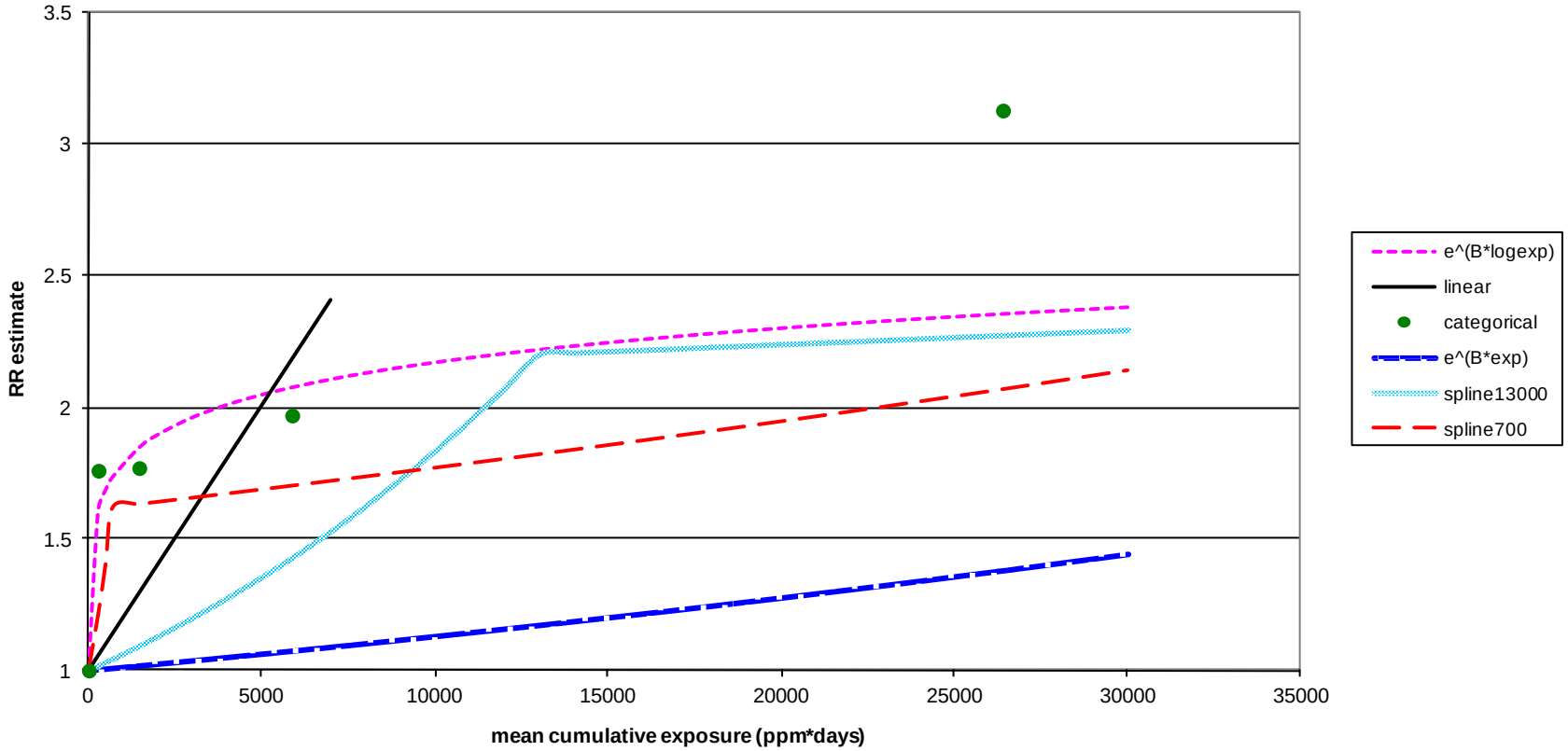

Figure 4-3. RR estimate for breast cancer mortality vs. mean exposure (with 20-year lag, unadjusted for continuous exposure).

e^(B*exp): Cox regression results for RR = $e^{(\beta \times \text{exposure})}$; e^(B*logexp): Cox regression results for RR = $e^{(\beta \times \ln(\text{exposure}))}$; categorical: Cox regression results for RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures; linear: weighted linear regression of categorical results, excluding highest exposure group (see text); spline700(13000): 2-piece log-linear spline model with knot at 700 (13,000) ppm × days (see text).
Source: Steenland reanalyses with 20-year lag; see Section D.2 of Appendix D (except for linear regression of the categorical results, which was done by EPA).

For the two-piece log-linear spline modeling approach, as described in Section 4.1.1.2 and discussed more fully in Section D.2 of Appendix D, the Cox regression model was the underlying basis for the splines which were fit to the breast cancer mortality exposure-response data (cumulative exposure is used here, with a 20-year lag), and thus, log RR is a function of two lines which join at a single point of inflection, called a "knot." The shape of the two-piece log-linear spline model, in particular the slope in the low-exposure region, depends on the location of the knot. For this assessment, knot selection was first attempted by trying different knots in increments of 1,000 ppm × days, starting at 1,000 ppm × days, and choosing the one that resulted in the largest model likelihood. The model likelihood did not actually change much across the different trial knots (see Figure D-2a of Appendix D), but it did change slightly, and this approach indicated that a knot of 13,000 ppm × days for the breast cancer mortality data yielded the largest likelihood.[22] However, a visual inspection of the model fit suggested that the two-piece log-linear spline model with a knot at 13,000 ppm × days underestimates the low-exposure results (see Figure 4-3). Thus, knots below 1,000 ppm × days in increments of 100 ppm × days were investigated, and it was revealed that a knot at 700 ppm × days yielded a model with a likelihood that exceeded that for the model with the knot at 13,000 ppm × days (see Figures D-2a and D-2a' of Appendix D).[23] The model with the knot at 700 ppm × days, however, has a seemingly implausibly steep low-exposure slope, as was the case with the largest likelihood models for the lymphohematopoietic cancers above. Moreover, neither the model with the knot at 700 ppm × days nor the one with the knot at 13,000 ppm × days was statistically significant overall, although both were nearly so (p = 0.067 and 0.074, respectively). See Table 4-8 and Section D.2 of Appendix D for parameter estimates and fit statistics for the two spline models. Because there was low confidence in the steep low-exposure slope from the two-piece spline model with the largest likelihood, which is based on a relatively small number of cases in that exposure range, and because the model with the knot at 13,000 ppm × days, which had a local largest likelihood, appeared to have a poor fit to the low-exposure data, it was determined that the weighted linear regression of the categorical results was more appropriate as the basis for the unit risk estimates. For more discussion of the breast cancer mortality exposure-response modeling using the continuous data, see Section D.2 of Appendix D.

For the weighted linear regression, the results from the Cox regression model with categorical cumulative exposure (and a 20-year lag) presented in Table 4-7 were used, excluding

[22]Using the log-linear spline model with the knot at 13,000 ppm × days, a regression coefficient of 0.0000607 per ppm × day (SE = 0.0000309 per ppm × day) was obtained for the low-exposure spline segment (see Appendix D).
[23]Using the optimal two-piece log-linear spline model with the knot at 700 ppm × days, a regression coefficient of 0.0006877 per ppm × day (SE = 0.0004171 per ppm × day) was obtained for the low-exposure spline segment (see Appendix D).

the highest exposure group, and the approach discussed above for the lymphoid cancers (see Section 4.1.1.2).[24] Mean and median exposures for the cumulative exposure groups were provided by Dr. Steenland (see Appendix D).[25] See Table 4-8 for the results obtained from the weighted linear regression of the categorical results and mean exposures and Figure 4-3 for a depiction of the resulting linear regression model.

The linear regression of the categorical results and the actuarial program (life-table analysis) were used to estimate the exposure level (EC_x) and the associated 95% lower confidence limit (LEC_x) corresponding to an extra risk of 1% ($x = 0.01$). As discussed in Section 4.1.1.2, a 1% extra risk level is a more reasonable response level for defining the POD for these epidemiologic data than 10%.

Table 4-8. Exposure-response modeling results for breast cancer mortality in females in the NIOSH cohort for models not presented by Steenland et al. (2004)

Model[a]	*p* value	Coefficient (SE)
Optimal 2-piece log-linear spline (knot at 700 ppm × days)	0.067	low-exposure spline segment: B1 = 0.000688 (0.000417)
Alternate 2-piece log-linear spline (knot at 13,000 ppm × days)	0.074	low-exposure spline segment: B1 = 0.0000607 (0.0000309)
Linear regression of categorical results, excluding the highest exposure quartile	0.09	0.000201 (0.000120)

[a]All with cumulative exposure in ppm × days as the exposure variable and with a 20-yr lag; based on 103 breast cancer deaths.
[b]*p*-values from likelihood ratio test, except for linear regression of categorical results, where Wald *p*-values are reported.

Source: Additional analyses performed by Dr. Steenland (see Section D.2 of Appendix D), except for the linear regression of the categorical results, which was performed by EPA.

Because EtO is DNA-reactive and has direct mutagenic activity (see Section 3.3.3), which is one of the cases cited by EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) for the use of linear low-dose extrapolation, a linear low-exposure extrapolation was

[24]Equations for this weighted linear regression approach are presented in Rothman (1986) and summarized in Appendix F.
[25]Mean exposures for females with a 20-year lag for the categorical exposure quartiles in Table 8 of Steenland et al. (2004) 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.

performed. The EC_{01}, LEC_{01}, and inhalation unit risk estimate calculated for breast cancer mortality from the linear regression model of the categorical results are presented in Table 4-9. The resulting unit risk estimate for breast cancer mortality based on the linear regression of the categorical results using cumulative exposure with a 20-year lag is 0.513 per ppm. EC_{01} and LEC_{01} estimates from the other models considered are presented for comparison only, to illustrate the differences in model behavior at the low end of the exposure-response range. Unit risk estimates are not presented for these other models because, as discussed above, these models were deemed unsuitable for the derivation of risks from (low) environmental exposure levels. As one can see, the standard Cox regression cumulative exposure model, with its extreme sublinearity in the lower exposure region, yields a substantially higher EC_{01} estimate (0.530 ppm) than the EC_{01} estimate of 0.0387 ppm from the linear regression of the categorical results, while the log cumulative exposure Cox regression model, with its extreme supralinearity in the lower exposure region, yields a substantially lower EC_{01} estimates (0.00112 ppm). The estimates from the two-piece log-linear spline models flank the result from the linear regression of the categorical results more closely. The steep low-exposure segment of the two-piece log-linear spline model with the optimal knot at 700 ppm × days yields an EC_{01} estimate of 0.00941 ppm, whereas the shallower low-exposure slope from the two-piece log-linear spline model with the local maximum likelihood suggesting a knot at 13,000 ppm × days yields an EC_{01} estimate of 0.107 ppm. Converting the units, the unit risk estimate of 0.513 per ppm for breast cancer mortality from the linear regression model of the categorical results corresponds to a unit risk estimate 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, especially for cancer types with good survival rates, such as breast cancer. 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 one can estimate cancer incidence risks directly rather than estimate them from mortality data. The incidence study used a (sub)cohort of 7,576 (76%) of the female workers from the original cohort. Cohort eligibility for the incidence study 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. Interviews were sought from all the women in the incidence study cohort or their next-of-kin (18% of the cohort had died). Completed interviews were obtained for 5,139 (68%) of the

Table 4-9. EC_{01}, LEC_{01}, and unit risk estimates for breast cancer mortality in females[a]

Model	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Log cumulative exposure, 20-yr lag[b]	0.00112	0.000219	--[c]
Cumulative exposure, 20-yr lag[d]	0.530	0.285	--[c]
Low-exposure log-linear spline, cumulative exposure with knot at 700 ppm × days, 20-yr lag[e]	0.00941	0.00471	--[c]
Low-exposure log-linear spline, cumulative exposure with knot at 13,000 ppm × days, 20-yr lag[f]	0.107	0.0580	--[c]
Categorical; cumulative exposure, 20-yr lag[g]	0.0387	0.0195	**0.513**

[a]From lifetime continuous exposure. Unit risk = $0.01/LEC_{01}$.
[b]From Table 8 of Steenland et al. (2004), Cox regression model.
[c]Unit risk estimates are not presented for these models because these models were deemed unsuitable for the derivation of risks from (low) environmental exposure levels (see text).
[d]From Dr. Steenland's reanalyses (see Table D-2d of Appendix D), Cox regression model.
[e]From low-exposure segment of two-piece log-linear spline model with largest model likelihood and a knot at 700 ppm × days; see text and Table D-2c of Appendix D. The EC_{01} value is below the value of 0.009 ppm roughly corresponding to the knot of 700 ppm × days [(700 ppm × days) × (10 m^3/20 m^3) × (240 d/365 d) × (365 d/yr)/70 yr = 0.0013 ppm] and, thus, appropriately in the range of the low-exposure segment.
[f]From low-exposure segment of two-piece log-linear spline model with a local largest likelihood for knot at 13,000 ppm × days; see text and Table D-2f of Appendix D. The EC_{01} value is below the value of 0.17 ppm roughly corresponding to the knot of 13,000 ppm × days (see calculation in footnote e) and, thus, appropriately in the range of the low-exposure segment.
[g]Regression coefficient derived from linear regression of categorical Cox regression results from Table 8 of Steenland et al. (2004), as described in Section 4.1.2.2. The EC_{01} value is appropriately below the value of 0.064 ppm roughly corresponding to the value of about 5,000 ppm × days (see footnote e for calculation) above which the linear regression model of the categorical results does not apply (see Figure 4-3).

7,576 women in the cohort. The investigators also attempted to acquire breast cancer incidence data for the cohort 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 cohort (*n* = 7,576) and the subcohort of women with interviews (*n* = 5,139). For additional details and discussion of the Steenland et al. (2003) study, see Section A.2.16 of 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 4.1.1.1 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.

From the Steenland et al. (2003) internal analyses (Cox regression) 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 4-10, and these are the results considered 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 initial 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 more complete case ascertainment and has additional information available on potential breast cancer confounders.

For the actuarial program (life-table analysis), U.S. age-specific all-cause mortality rates for 2004 for females of all race groups combined (Arias, 2007) 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* being diagnosed with breast cancer in a given age interval. All-cause mortality rates and breast cancer incidence rates were summed, and breast cancer mortality rates

Table 4-10. Cox regression results for breast cancer incidence in females from the NIOSH cohort, for the models presented by Steenland et al. (2003)[a,b]

Cohort	Exposure variable[c]	Coefficient (SE), *p*-value[d]	ORs by category[e] (95% CI)
Full incidence study cohort *n* = 7,576 319 cases	Cumulative exposure, 15-yr lag	0.0000054 (0.0000035), *p* = 0.12	
	Log cumulative exposure, 15-yr lag	0.037 (0.019), *p* = 0.05	
	Categorical cumulative exposure, 15-yr 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-yr lag	0.0000095 (0.0000041), *p* = 0.02	
	Log cumulative exposure, 15-yr lag	0.050 (0.023), *p* = 0.03	
	Categorical cumulative exposure, 15-yr lag	--[f]	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 yr of birth (quartiles). Subcohort models include cumulative exposure, categorical variables for yr of birth (quartiles), breast cancer in first-degree relative, and parity.
[c]Cumulative exposure is in ppm × days.
[d]*p*-values for exposure variable from Wald test, as reported by Steenland et al. (2003).
[e]Exposure categories are 0, >0–647, 647–2,026, 2,026–4,919, 4,919–14,620, >14,620 ppm × days.
[f]*p*-value for the addition of the categorical exposure variables = 0.11 (email dated 5 March 2010 from Kyle Steenland, Emory University, to Jennifer Jinot, EPA).

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

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 2002–2006 mortality rates for invasive breast cancer in females were obtained from a SEER report (Horner et al., 2009). The SEER report also provided SEER-17 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's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) 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 were 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 in Section 4.1.1.2 above.

For breast cancer incidence in both the full cohort (see Figure 4-4) and the subcohort with interviews (see Figure 4-5), the low-exposure categorical results suggest a more linear low-exposure exposure-response relationship than that obtained with either the continuous variable log cumulative exposure (supralinear) or cumulative exposure (sublinear) Cox regression models, the two of which lie on opposite sides of the low-exposure categorical results. Thus, as with the lymphohematopoietic cancer and the breast cancer mortality results above, EPA proposed in the 2006 Draft Assessment (U.S. EPA, 2006a), which relied on the original published results of Steenland et al. (2003), 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 RR estimates for the highest exposure quintiles suggest somewhat supralinear exposure-response relationships for both the full cohort and the subcohort with interviews and supralinearity is evidenced in the subcohort with interviews by the strong influence of the top 5% of cumulative exposures on dampening the slope of the [cumulative exposure] Cox regression model [see Section D.1 and Figure D-1d of Appendix D]. Moreover, there is more uncertainty in using the mean cumulative exposure to represent the range of exposures in a highest exposure categorical group because such groups contain a wider range of exposures; for example, for the subcohort with interviews, the highest exposure quintile contains exposures ranging from about 14,500 ppm × days to over 250,000 ppm × days). Linear modeling of categorical (i.e., grouped) epidemiologic data and elimination of the highest exposure group(s) under certain circumstances to obtain a better fit of low-exposure data are both standard techniques used in EPA dose-response assessments (U.S. EPA, 2012, 2005a). However, as discussed in Section 4.1.1.2 for the lymphohematopoietic cancer data, the SAB panel that reviewed the draft assessment recommended that EPA not rely on the published grouped data but, rather, do additional analyses using the individual data (SAB, 2007).

Consequently, it was determined that using the individual data, a better way to address the apparent supralinearity of the data (while avoiding the extreme low-exposure curvature obtained with the log cumulative exposure Cox regression model) might be to use a two-piece

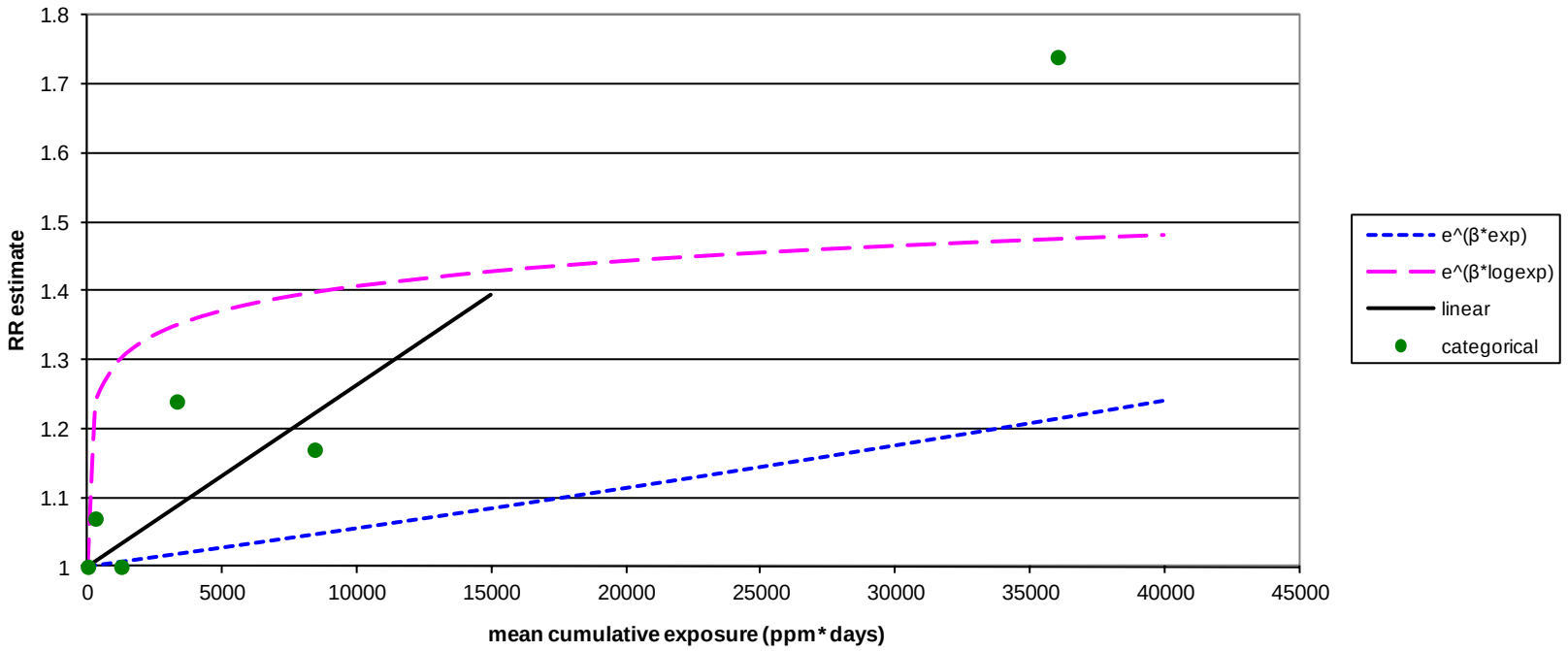

Figure 4-4. RR estimate for breast cancer incidence in full cohort vs. mean exposure (with 15-year lag, unadjusted for continuous exposure).

e^(β*exp): Cox regression results for RR = $e^{(\beta \times \text{exposure})}$; e^(β*logexp): Cox regression results for RR = $e^{(\beta \times \ln(\text{exposure}))}$; categorical: Cox regression results for RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures; linear: weighted linear regression of categorical results, excluding highest exposure group (see text).

Source: Steenland et al. (2003) (except for linear regression of the categorical results, which was done by EPA).

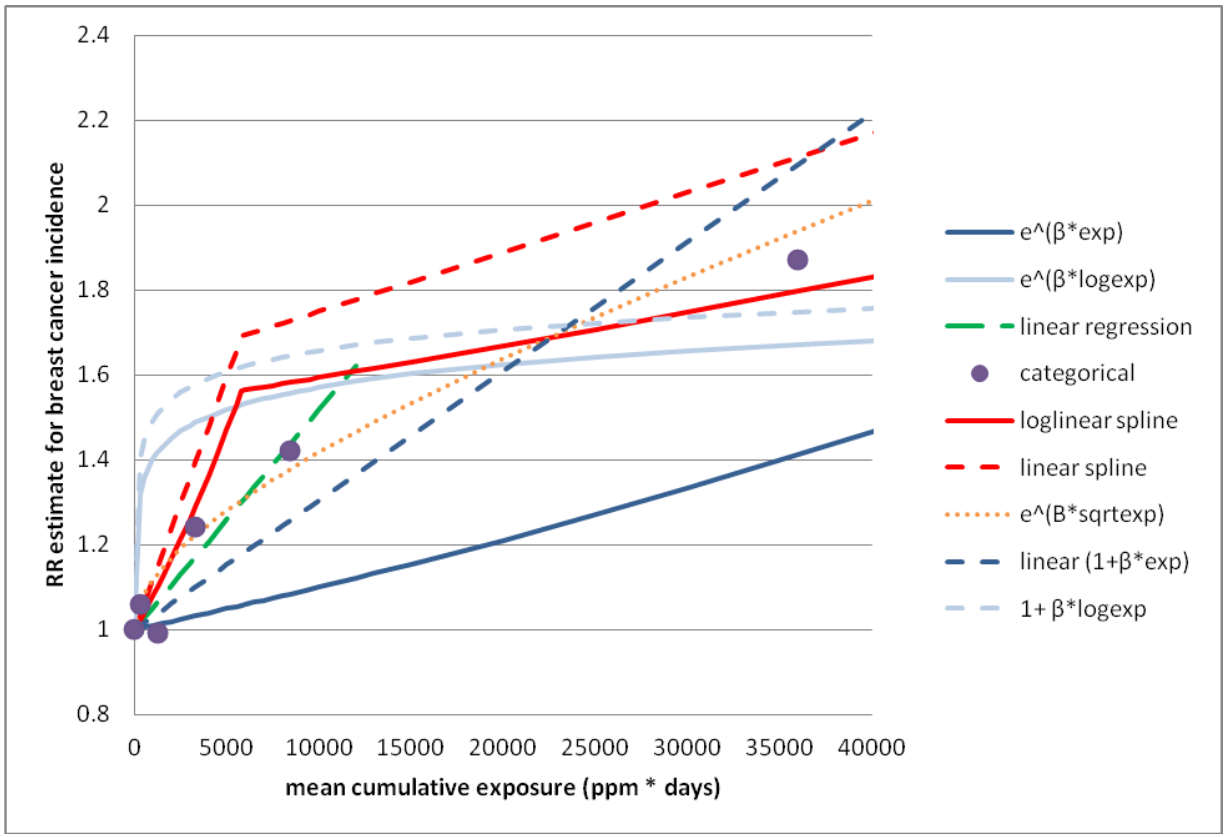

Figure 4-5. RR estimate for breast cancer incidence in subcohort with interviews vs. mean exposure (with 15-year lag, unadjusted for continuous exposure).

e^(β*exp): Cox regression results for RR = $e^{(\beta \times \text{exposure})}$; e^(β*logexp): Cox regression results for RR = $e^{(\beta \times \ln(\text{exposure}))}$; categorical: Cox regression results for RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures; e^(β*sqrtexp): Cox regression results for RR = $e^{(\beta \times \text{sqrt}(\text{exposure}))}$; linear regression: weighted linear regression of categorical results, excluding highest exposure group (see text); log-linear and linear spline: 2-piece spline models, both with knots at 5,800 ppm × days (see text); linear: RR = 1 + β × exposure, with exposure as a continuous variable; 1 + β*logexp: RR = 1 + β × ln(exposure), exposure continuous.

Sources: Steenland et al. (2003) except for Steenland 2-piece spline models (see Appendix D) and linear regression of the categorical results, which was done by EPA.

spline model, and Dr. Steenland was commissioned to do the spline analyses. His findings are reported in Appendix D (see Section D.1), and the results for the breast cancer incidence analyses are summarized below. Note that, for the two-piece spline analyses, only the data from the subcohort with interviews and for the invasive and in situ breast cancers combined were analyzed, because this was the preferred data set, as discussed above. (Dr. Steenland also employed a cubic spline model as a semiparametric approach to visualize the underlying exposure-response relationship; however, this approach produces an overly complicated function for an empirical model, as opposed to a biologically based model, and was not used for risk assessment purposes. In addition, Dr. Steenland investigated the use of a Cox regression model with a square-root transformation of cumulative exposure; however, this approach, though less extreme than using the log transformation of cumulative exposure, also yields a notably supralinear model [see Figure 4-5], which can result in unstable low-exposure risk estimates. The model results for both the cubic spline and square-root transformation models are included in Appendix D, Section D.1, but are not considered further here. EPA chose to pursue the development of two-piece spline models, which avoid the problem of unstable risk estimates from supralinear curvature in the low-exposure region and provide a more general approach to modeling supralinear exposure-response data, as opposed to using random, arbitrary power-transformations of the exposure variable.)

For the two-piece log-linear spline modeling approach, as described in Section 4.1.1.2 and discussed more fully in Appendix D, the Cox regression model was the underlying basis for the splines which were fit to the breast cancer incidence exposure-response data (cumulative exposure is used here, with a 15-year lag), and, thus, log RR is a function of two lines which join at a single point of inflection, called a "knot." The shape of the two-piece spline model, in particular the slope in the low-exposure region, depends on the location of the knot. For this assessment, the knot was generally selected by trying different knots in increments of 1,000 ppm × days, starting at 1,000 ppm × days, and choosing the one that resulted in the largest model likelihood. In some cases, increments of 100 ppm × days were used between the increments of 1,000 ppm × days to fine-tune the knot selection. The model likelihood did not actually change much across the different trial knots (see Figure D-1a of Appendix D), but it did change slightly, and a knot of 5,800 ppm × days for the breast cancer incidence data based on the largest likelihood was chosen. The two-piece log-linear spline model with this knot provided a statistically significant fit to the data ($p = 0.01$ for the addition of the exposure terms), as well as a good visual fit (see Figure 4-5).

A two-piece linear spline model was also fitted, using the just-published approach of Langholz and Richardson (2010). This model is similar to the log-linear spline model discussed

above; however, for the linear spline model, the underlying basis for the splines is a linear model (i.e., RR = 1 + β × *z*, where *z* represents the covariate data, including exposure, and β are the parameters being estimated). The knot was selected as for the log-linear spline model, and the same knot of 5,800 ppm × days yielded the largest likelihood (see Figure D-1h of Appendix D) and was also chosen for the two-piece linear spline model. The two-piece linear spline model with this knot provided a statistically significant fit to the data ($p = 0.002$ for the addition of the exposure terms), as well as a good visual fit (see Figure 4-5). Because this model provided a better fit than the log-linear spline model, i.e., it had a lower AIC, the two-piece linear spline model was selected as the preferred model for the unit risk estimates for breast cancer incidence. See Table 4-11 and Section D.1 of Appendix D for parameter estimates and fit statistics for the two spline models.

Table 4-11. Exposure-response modeling results for breast cancer incidence in females from the NIOSH cohort for models not presented by Steenland et al. (2003)

Model[a]	*p* value[b]	Coefficient (SE)
Full incidence study cohort[c]		
Linear regression of categorical results, excluding the highest exposure quintile	0.33	0.0000264 (0.0000269)
Subcohort with interviews[d]		
2-piece log-linear spline (knot at 5,800 ppm × days)	0.01	low-exposure spline segment: B1 = 0.0000770 (0.0000317)
2-piece linear spline (knot at 5,800 ppm × days)	0.002	low-exposure spline segment: B1 = 0.000119 (0.0000677)
linear	0.003	0.0000304 (0.0000175)
linear with log cumulative exposure	0.01	0.0713 (0.0392)
Linear regression of categorical results, excluding the highest exposure quintile	0.16	0.0000517 (0.0000369)

[a]All with cumulative exposure in ppm × days as the exposure variable and with a 15-yr lag.
[b]*p*-value for addition of exposure variables from likelihood ratio test, except for the linear regressions of categorical results, where Wald *p*-values are reported.
[c]319 breast cancer cases.
[d]233 breast cancer cases.

Source: Additional analyses performed by Dr. Steenland (see Section D.2 of Appendix D), except for the linear regressions of categorical results, which were performed by EPA using the equations of Rothman (1986) presented in Appendix F.

Linear RR models with cumulative exposure and log cumulative exposure as continuous variables were also investigated using the approach of Langholz and Richardson (2010), and these models fit better than the corresponding log RR models (see Table 4-11 and Section D.1 of Appendix D) although not as well as the two-piece linear spline model, which had the lowest AIC. Risk estimates based on the linear model with cumulative exposure are developed for comparison, but the linear model with log cumulative exposure is too steep in the low-exposure region (see Figure 4-5) and is not considered further. For more details of the breast cancer incidence exposure-response modeling, see Section D.1 of Appendix D.

Risk estimates based on the original linear regression analyses of the categorical results are also presented for comparison. For the approach of using a weighted linear regression of the results from the Cox regression model with categorical cumulative exposure (and a 15-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.[26] Mean and median exposures for the cumulative exposure groups for the full cohort were kindly provided by Dr. Steenland (email dated April 21, 2004, from Kyle Steenland, Emory University, to Jennifer Jinot, EPA).[27] 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 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. See Table 4-11 for the results from the weighted linear regressions of the categorical results and Figures 4-4 and 4-5 for a depiction of the resulting linear regression models.

As the subcohort with interviews from the NIOSH incidence study cohort provides the preferred data set for the derivation of unit risk estimates for breast cancer, a summary of all the models considered for modeling the breast cancer exposure-response data from the subcohort and the judgments made about model selection is provided in Table 4-12. See Figure 4-5 for visual representations of the models. See Tables 4-10 and 4-11 and Section D.1 of Appendix D for parameter estimates, *p*-values, and other fit statistics. Three of the models presented in

[26]Equations for this weighted linear regression approach are presented in Rothman (1986) and summarized in Appendix F.

[27]Mean exposures for females with a 15-year lag for the exposure categories in Table 3 of Steenland et al. (2003) 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.

Table 4-12. Models considered for modeling the exposure-response data for breast cancer incidence in females in the subcohort with interviews from the NIOSH incidence study cohort for the derivation of unit risk estimates

Model[a]	AIC[b]	Comments
Cox regression (log-linear) model	1956.675	Good overall statistical fit but poor visual fit (too shallow) in the low-exposure region.
Cox regression model with log cumulative exposure	1956.176	Good overall statistical fit but too steep in the low-exposure region.
Cox regression model with square-root transformation of exposure	1953.028	Good overall statistical fit but still notably supralinear (steep) in the low-exposure region, though less so than with the log transformation; also preference was given to the two-piece spline models as providing a more general approach to modeling supralinear data.
Linear regression of categorical results, excluding the highest exposure quintile	--[c]	Not statistically significant, though that is unsurprising since the approach, which is based on categorical data, has low statistical power; preference given to models that treated exposure as a continuous variable, as recommended by the SAB, and that also provided reasonable representations of the low-exposure region.
2-piece log-linear spline model (knot at 5,800 ppm × days)	1954.485	Good overall statistical fit and good visual fit; preference given to the 2-piece linear spline model because it had a better statistical fit (lower AIC) and better apparent fit to the lower-exposure data.
linear model (RR = 1 + β × exposure)	1952.260	Good overall statistical fit and good visual fit; preference given to the 2-piece linear spline model because it had a better statistical fit (lower AIC) and better apparent fit to the lower-exposure data.
linear model with log cumulative exposure	1954.267	Good overall statistical fit but too steep in the low-exposure region.
2-piece linear spline model (knot at 5,800 ppm × days)	1950.935	SELECTED. Good overall statistical fit and good visual fit; lower AIC than 2-piece log-linear spline and linear model and better apparent fit to the lower-exposure data.

[a]All with cumulative exposure as the exposure variable, except where noted, and with a 15-yr lag.
[b]AIC = 2p-2LL, where p = # of parameters and LL = ln(likelihood), assuming two exposure parameters for the two-piece spline models.
[c]Not calculated.

Table 4-12 had a good overall statistical fit, a good visual fit, and a credible low-exposure slope (the linear and log-linear two-piece spline models and the [continuous] linear RR model). To better compare these models, they are plotted again in Figure 4-6 this time against the categorical data in deciles. Earlier categorical results in this assessment were based on the (log-linear) Cox regression model; however, the deciles in Figure 4-6 are based on a linear RR categorical model—this model had a lower AIC than the log-linear decile model (1963.94 vs. 1966.91), and it provides a statistically significant fit to the data ($p = 0.004$), so the deciles should provide a good representation of the data for the purposes of comparing the models (the decile results from the log-linear and linear RR categorical models and the mean cumulative exposure estimates for the deciles are presented in Section D.1 of Appendix D). As can be seen in Figure 4-6, the two-piece linear spline model, in addition to having the lowest AIC (see Table 4-12), appears to have a better fit to the lower-exposure data, which are of the greatest interest in estimating low-exposure risk. It also appears from Figure 4-6 that the linear model has a poorer fit to the lower-exposure data than either of the two-piece spline models. This is consistent with the analysis presented in Section D.1 of Appendix D showing the strong influence of the upper tail of cumulative exposures on the results of the cumulative exposure Cox regression model. The responses in the upper tail of exposures are relatively dampened, such that when the highest 5% of exposures are excluded, the slope of the Cox regression model is substantially increased (e.g., at 10,000 ppm × days, the RR estimate increases from about 1.1 to almost 1.5; see Figure D-1d in Appendix D). This strong influence of the upper tail of exposures would similarly attenuate the slope of the (continuous) linear model. The two-piece spline models, on the other hand, are more flexible, and the influence of the upper tail of exposures would be primarily on the upper spline segment; thus, the two-piece models are able to provide a better fit to the lower-exposure data.

The exposure level (EC_x) and the associated 95% lower confidence limit (LEC_x) corresponding to an extra risk of 1% ($x = 0.01$) for breast cancer incidence in females (based on invasive + in situ tumors in the subcohort with interviews) for the models discussed above were estimated using the actuarial program (life-table analysis). As noted in Section 4.1.1.2, a 1% extra risk level is a more reasonable response level for defining the POD for these epidemiologic data than a 10% level. The results are presented in Table 4-13.

Because EtO is DNA-reactive and has direct mutagenic activity (see Section 3.3.3), which is one of the cases cited by EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) for the use of linear low-dose extrapolation, a linear low-exposure extrapolation was performed. The inhalation unit risk estimates for the different breast cancer incidence models considered suitable for low-exposure extrapolation are presented in Table 4-13. As discussed

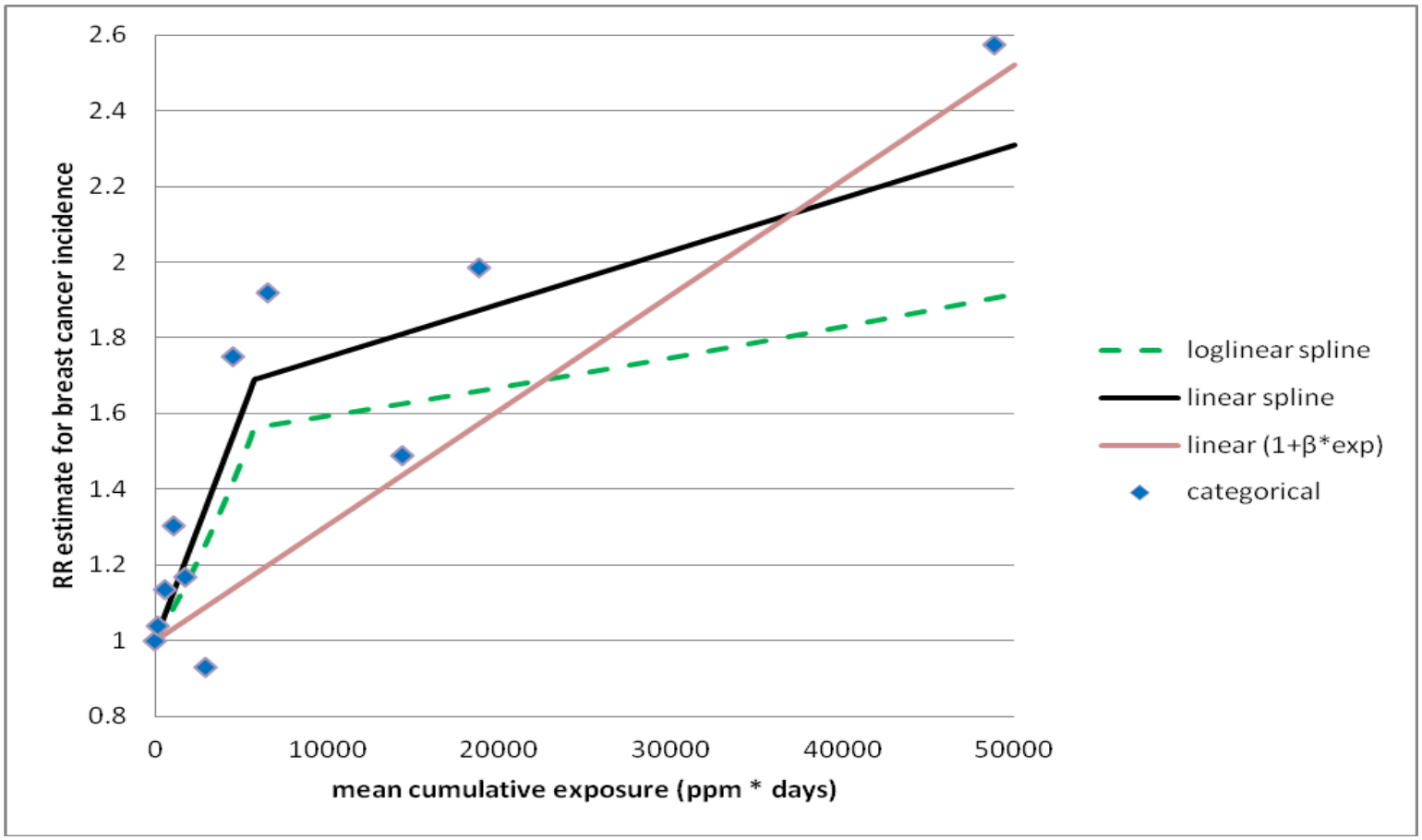

Figure 4-6. RR estimate for breast cancer incidence in subcohort with interviews vs. mean exposure (with 15-year lag, unadjusted for continuous exposure); select models compared to deciles.

Categorical: linear model (RR = 1 + β × exposure) with categorical exposures; log-linear and linear spline: 2-piece spline models, both with knots at 5,800 ppm × days (see text); linear: RR = 1 + β × exposure, with exposure as a continuous variable.
Sources: Steenland analyses in Appendix D.

Table 4-13. EC_{01}, LEC_{01}, and unit risk estimates for breast cancer incidence in females—invasive and in situ[a]

Model	With interviews			Full cohort		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Cox regression, cumulative exposure, 15-yr lag[b]	0.135	0.0788	--[c]	0.237	0.115	--[c]
Cox regression, log cumulative exposure, 15-yr lag[b]	0.0000765	0.0000422	--[c]	0.000124	0.0000529	--[c]
Linear regression of categorical results, excluding highest exposure quintile; cumulative exposure, 15-yr lag[b,d]	0.0257	0.0118	0.847	0.0503	0.0188	0.532
Low-exposure log-linear spline, cumulative exposure, 15-yr lag[e]	0.0166	0.00991	1.01[f]	--[g]		
Linear model with continuous cumulative exposure, 15-yr lag[h]	0.0437	0.0224	0.446[i]	--[g]		
Low-exposure linear spline, cumulative exposure, 15-yr lag[e]	0.0112	0.00576	**1.74**[f,j]	--[g]		

[a]All-cause mortality adjusted (to dying of something other than breast cancer or developing breast cancer). Unit risk = $0.01/LEC_{01}$. Note that the EC_{01} and LEC_{01} results presented here will not exactly match those presented in Appendix D because, although the regression coefficients reported by Dr. Steenland in Appendix D were used, the life-table analyses using 2004 all-cause mortality and 2002–2006 cause-specific mortality and incidence rates were redone to be more up-to-date; the results presented in Appendix D were based on life-table analyses using 2000 all-cause mortality rates and comparable cause-specific rates.

[b]From Tables 4 and 5 of Steenland et al. (2003), Cox regression models.

[c]Unit risk estimates are not presented for these models because these models were deemed unsuitable for the derivation of risks from (low) environmental exposure levels (see text).

[d]Regression coefficient derived from linear regression of categorical results, as described in Section 4.1.2.3.

Table 4-13. EC_{01}, LEC_{01}, and unit risk estimates for breast cancer incidence in females—invasive and in situ[a] (continued)

[e]From low-exposure segment of two-piece spline analysis; see text and Table D-1c of Appendix D for log-linear model or Table D-1i for linear model; two-piece spline analyses not performed for the full cohort. The EC_{01} value is below the value of 0.075 ppm roughly corresponding to the knot of 5,800 ppm × days [(5,800 ppm × days) × (10 m^3/20 m^3) × (240 d/365 d) × (365 d/yr)/70 yr = 0.075 ppm] and, thus, appropriately in the range of the low-exposure segment.
[f]For unit risk estimates above 1, convert to risk per ppb (e.g., 1.74 per ppm = 1.74×10^{-3} per ppb).
[g]Not estimated.
[h]From linear analyses in Section D.1.b.2 and Table D-1i of Appendix D.
[i]Confidence intervals used in deriving the LEC_{01}s were estimated employing the Wald approach. Confidence intervals for linear RR models, however, in contrast to those for the log-linear RR models, may not be symmetrical. EPA also evaluated application of a profile likelihood approach for the linear RR models (Langholz and Richardson, 2010), which allows for asymmetric CIs, for comparison with the Wald approach. The MLE for the regression coefficient of the linear model is 0.0000304 per ppm × day. Using the profile likelihood method, the (95% one-sided) upper bound on the regression coefficient is 0.0000745 per ppm × day and the (95% one-sided) lower bound on the regression coefficient is 0.00000975 per ppm × day. Based on these profile likelihood estimates, the LEC_{01} estimate is 0.0174 ppm, the UEC_{01} estimate is 0.133 ppm, and the unit risk estimate for breast cancer incidence from the linear model would have been 0.575 per ppm, slightly higher (29%) than the value of 0.446 per ppm obtained using the Wald approach.
[j]Confidence intervals used in deriving the LEC_{01}s were estimated employing the Wald approach. Confidence intervals for linear RR models, however, in contrast to those for the log-linear RR models, may not be symmetrical. EPA also evaluated application of a profile likelihood approach for the linear RR models (Langholz and Richardson, 2010), which allows for asymmetric CIs, for comparison with the Wald approach. The MLE for the regression coefficient of the first spline segment is 0.000119 per ppm × day. Using the profile likelihood method, the (95% one-sided) upper bound on the regression coefficient is 0.000309 per ppm × day and the (95% one-sided) lower bound on the regression coefficient is 0.000032 per ppm × day. Based on these profile likelihood estimates, the LEC_{01} estimate is 0.00430 ppm, the UEC_{01} estimate is 0.0415 ppm, and the unit risk estimate for breast cancer incidence from the low-exposure linear spline would have been 2.33 per ppm, slightly higher (34%) than the value of 1.74 per ppm obtained using the Wald approach.

above, the unit risk estimate based on the two-piece linear spline model using cumulative exposure with a 15-year lag (i.e., 1.74 per ppm, or 1.74×10^{-3} per ppb) is the preferred estimate. The two-piece log-linear spline model resulted in a unit risk estimate of 1.01 per ppm, while the linear regression of categorical results yielded a unit risk estimate of 0.847 per ppm and the continuous linear model produced a unit risk estimate of 0.446 per ppm; these alternate estimates are about 60%, 50%, and 25%, respectively, of the estimate based on the preferred two-piece linear spline model. EC_{01} and LEC_{01} estimates from the other models examined are presented for comparison only, to illustrate the differences in model behavior at the low end of the exposure-response range. Unit risk estimates are not presented for these other models because, as discussed above, the log cumulative exposure Cox regression model was considered overly supralinear and the cumulative exposure Cox regression model was considered overly sublinear for the data in the lower exposure range (e.g., first 4 quintiles of exposure). As one can see from the results for the subcohort with interviews, the standard Cox regression cumulative exposure

model, with its extreme sublinearity in the lower exposure region, yields a notably higher EC_{01} estimate (0.135 ppm) than that from the two-piece linear spline model (0.0112 ppm), while the log cumulative exposure model, with its extreme supralinearity in the lower exposure region, yields a substantially lower EC_{01} estimate (0.0000765 ppm). Converting the units, the preferred unit risk estimate of 1.74 per ppm corresponds to an estimate of 9.51×10^{-4} per $\mu g/m^3$ for breast cancer incidence.

As discussed above, the primary risk calculations for breast cancer incidence were based on invasive and in situ tumors in the subcohort of women with interviews, and the primary model was the two-piece linear spline model. For this assessment, the two-piece spline analyses were not performed with the full cohort and the life-table analyses were not replicated for the invasive cancers only. In the 2006 Draft Assessment (U.S. EPA, 2006a), however, comparison analyses were done. Using the linear regression of the categorical results, the comparable unit risk estimate for the full cohort was about 40% lower than the estimate based on the subcohort with interviews. The corresponding unit risk estimate derived based on the subcohort results but using invasive breast cancer only for the background incidence rates was about 17% lower than the estimate based on invasive and in situ tumors, 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 **1.74 per ppm** (1.74×10^{-3} per ppb) 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. Furthermore, the two-piece linear spline model, which uses the complete data set with exposure as a continuous variable, was statistically significant and had the lowest AIC and the best apparent visual fit to the lower-exposure data of the models considered. Converting the units, 1.74 per ppm corresponds to a unit risk of 9.51×10^{-4} per $\mu g/m^3$.

4.1.3. Total Cancer Risk Estimates

According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), cancer risk estimates are intended to reflect total cancer risk, not site-specific cancer risk; therefore, an additional calculation was made to estimate the combined risk for (incident) lymphoid and breast cancers, because females would be at risk for both cancer types. Assuming that the cancer types are independent and that the risk estimates are approximately normally distributed, one can estimate the 95% UCL (one-sided) on the total risk as the 95% UCL on the sum of the maximum likelihood estimates (MLEs) of the risk estimates according to the formula

$$95\%\ \text{UCL} = \text{MLE} + 1.645(\text{SE}), \quad (4\text{-}3)$$

where MLE is the MLE of total cancer risk (i.e., the sum of the individual MLEs) and the SE of the sum of the MLEs is the square root of the sum of the individual variances (i.e., the variance of the sum is the sum of the variances, and the SE is the square root of the variance). First, an EC_{01} of 0.0078 ppm for the total cancer risk (i.e., lymphoid cancer incidence + breast cancer incidence) was estimated, as summarized in Table 4-14.

Table 4-14. Calculation of EC_{01} for total cancer risk

Cancer type	EC_{01} (ppm)	$0.01/EC_{01}$ (per ppm)	EC_{01} for total cancer risk (ppm)
Lymphoid	0.0254	0.394	--
Breast	0.0112	0.893	--
Total[a]	--	1.29	0.00775

[a]The total $0.01/EC_{01}$ value equals the sum of the individual $0.01/EC_{01}$ values; the EC_{01} for the total cancer risk then equals $0.01/(0.01/EC_{01})$.

Then, a unit risk estimate of 2.3 per ppm for the total cancer risk (i.e., lymphoid cancer incidence + breast cancer incidence) was derived, as shown in Table 4-15. An LEC_{01} estimate of 0.00441 ppm for the total cancer risk can be calculated as 0.01/(2.27 per ppm).

Table 4-15. Calculation of total cancer unit risk estimate

Cancer type	Unit risk estimate (per ppm)	$0.01/EC_{01}$ (per ppm)	SE[a] (per ppm)	Variance	Total cancer unit risk estimate (per ppm)	LEC_{01} for total cancer risk[d] (ppm)
Lymphoid	0.877	0.394	0.294	0.0864	--	--
Breast	1.74	0.893	0.515	0.265	--	--
Total	--	1.29	(0.593)[b]	0.351	2.27[c]	0.00441

[a]SE = (unit risk – $0.01/EC_{01}$)/1.645.
[b]The SE of the total cancer risk is calculated as the square root of the sum of the variances (next column), not as the sum of the SEs.
[c]Total cancer unit risk = 1.29 + 1.645 × 0.593.
[d]The LEC_{01} for the total cancer risk equals 0.01/(total cancer unit risk estimate).

Thus, the total cancer unit risk estimate is 2.3 per ppm (or 2.3×10^{-3} per ppb; 1.2×10^{-3} per $\mu g/m^3$). Recall that this is the unit risk estimate derived under the assumption that RR is independent of age (see Section 4.1.1.2). The preferred assumption of increased early-life susceptibility, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b), is considered in Section 4.4. While there are uncertainties regarding the assumption of a normal distribution of risk estimates, the resulting unit risk estimate is appropriately bounded in the roughly twofold range between estimates based on the sum of the individual MLEs (i.e., 1.29) and the sum of the individual 95% UCLs (i.e., unit risk estimates, 2.6), or more precisely in this case, between the largest individual unit risk estimate (1.74) and the sum of the unit risk estimates (2.6). Thus, any inaccuracy in the total cancer risk estimate resulting from the approach used to combine risk estimates across cancer types is relatively minor.

4.1.4. Sources of Uncertainty in the Cancer Risk Estimates

The two major sources of uncertainty in quantitative cancer risk estimates are generally interspecies extrapolation and high-dose to low-dose extrapolation. The risk estimates derived from the Steenland et al. (2003) and Steenland et al. (2004) and additional Steenland (see Appendix D) analyses are not subject to interspecies uncertainty because they are based on human data. Furthermore, the human-based estimates are less affected by high-dose to low-dose extrapolation than are 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, 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-exposure extrapolation that was used (U.S. EPA, 2005a).

Because of the existence of endogenous EtO (see Section 3.3.3.1), several members of the SAB panel that reviewed EPA's external review draft assessment felt that the exposure-response relationship for cancer at low exposures would be nonlinear and suggested that it would be consistent with EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) to present a nonlinear approach for "extrapolation" to lower exposures (SAB, 2007). EPA considered this suggestion but judged that the support for a nonlinear approach was inadequate. In brief, as discussed in Sections 3.1 through 3.3.3, EtO is a DNA-reactive, mutagenic, multisite carcinogen in humans and experimental species; as such, it has the hallmarks of a compound for which low-dose linear extrapolation is strongly supported under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). EPA's *Guidelines for*

Carcinogen Risk Assessment (U.S. EPA, 2005a) do provide for presenting alternate approaches when those alternatives have significant biological support; however, EPA's analysis of the arguments for using a nonlinear approach presented on page 23 and in Appendix C of the SAB report (SAB, 2007) did not find these arguments to be persuasive. The arguments posited by the SAB panel members who supported using a nonlinear approach were largely that (1) DNA adducts may show a nonlinear response when identical adducts are formed endogenously and (2) mutations do not have linear relationships with exposure but exhibit an "inflection point." However, as discussed in Section 3.3.3.1, recent data from Marsden et al. (2009) support a linear exposure-response relationship for EtO exposure and DNA adducts ($p < 0.05$) and demonstrate increases of DNA adducts from exogenous EtO exposure above those from endogenous EtO for very low exposures to exogenous EtO, providing direct evidence against argument (1). Moreover, Appendix C of the SAB report (SAB, 2007) presents two EtO-specific mutation data sets in support of argument (2); however, EPA's analysis of these data sets finds that they are in fact consistent with low-dose linearity. See the response to this comment under charge question 2.b in Appendix H for a more comprehensive discussion of EPA's consideration and rejection of a nonlinear approach and for the details of EPA's analysis of the two EtO mutation data sets.

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

Regarding exposure estimation, the NIOSH investigators conducted a detailed retrospective exposure assessment to estimate the individual worker exposures. They used extensive data from 18 facilities, spanning a number of years, to develop a regression model (Hornung et al., 1994; Greife et al., 1988) [see also Section A.2.8 for more details about the development and evaluation of the regression model]. The model accounted for 85% of the variation in average EtO exposure levels in an independent set of test data. In addition, the modeled estimates were not highly biased nor biased in one direction when compared to the predictions of a panel of 11 industrial hygiene experts familiar with EtO levels in the sterilization industry. Detailed work history data for the individual workers were collected for the 1987 follow-up (Steenland et al., 1991). For the extended follow-up (Steenland et al., 2004; Steenland et al., 2003), 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 follow-up. 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., 2004; Steenland et al., 2003). While the NIOSH regression model performed well in estimating exposures in validation tests (Hornung et al., 1994), there is, nonetheless, uncertainty associated with any retrospective exposure assessment, and this can affect the ability to discriminate among exposure-response models.

With respect to the lymphohematopoietic cancer response, it is not clear exactly which lymphohematopoietic cancer subtypes are related to EtO exposure, so analyses were done for both lymphoid cancers and all lymphohematopoietic cancers (Steenland et al., 2004). The associations observed for all lymphohematopoietic cancers was largely driven by the lymphoid cancer responses, and biologically, there is stronger support for an etiologic role for EtO in the development of the more closely related lymphoid cancers than in the development of the more diverse cancers in the aggregate all lymphohematopoietic cancer grouping; thus, the lymphoid cancer analysis is the preferred analysis for the lymphohematopoietic cancers. Nonetheless, the preferred unit risk estimate for all lymphohematopoietic cancers was similar to (about 50% greater than) that for the lymphoid cancers.

For the lymphoid cancer response (Steenland et al., 2004), modeling the exposure-response relationship is limited by the small number of cases (n = 53). The Cox proportional hazards model used by Steenland et al. (2004) 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* (U.S. EPA, 2005a), 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 at higher exposures, making it difficult to derive stable risk estimates (i.e., estimates that are not highly dependent on the POD). And the alternative cumulative exposure model, though typically used for epidemiologic data, is too sublinear in the low-exposure region for these data, which exhibit supralinearity. EPA attempted to fit two-piece log-linear and linear spline models to the individual continuous data to address the supralinearity of the data while avoiding the extreme low-exposure curvature of the log cumulative exposure model; however, these models

resulted in low-exposure slopes that appeared to be implausibly steep (i.e., they suggested excessively large changes in risk from small changes in exposure). The steep low-exposure slopes are a manifestation of apparently high risks in workers with relatively low exposures; however, this elevation is based on small numbers of cancer cases in that exposure range, and EPA has low confidence in the low-exposure slopes. The two-piece spline model with the knot at a higher exposure level could have been used, but without model likelihood as a basis for knot selection, such selection becomes arbitrary, and with the knot at the higher exposure level which had an apparent local maximum for the log-linear model (1,600 ppm × days rather than 100 ppm × days), the visual fit was poor (see Figure 4-1). Thus, EPA opted for a weighted linear regression model based on the Cox regression categorical results, excluding the highest exposure group, to reflect the exposure-response relationship in the exposure region below the "plateau." The all lymphohematopoietic cancer data set had more cases (n = 74) but was heavily dominated by the lymphoid cancer response and conveyed the same problems for exposure-response modeling; thus, a linear regression model, excluding the highest exposure group, was used for this data set as well.

The linear model is a parsimonious choice that assumes neither a sublinear nor a supralinear exposure-response relationship and acknowledges the inherent imprecision in the epidemiological data. The highest exposure group was excluded because it is less relevant to the low-exposure risks of interest for low-exposure extrapolation and its inclusion would have overly influenced the linear regression, resulting in a slope that would have substantially underestimated the apparent low-exposure risks. Excluding data can appear arbitrary, but EPA aimed to avoid an arbitrary selection by using the a priori exposure groups presented by Steenland et al. (2004) and excluding only the highest exposure group, with the exposures least relevant to low environmental exposure levels. The linear regression has its own limitations (e.g., it is based on categorical rather than continuous data and the slopes were not statistically significant); nonetheless, it was judged to be the most reasonable approach for deriving low-exposure risk estimates from the available lymphohematopoietic cancer data.

Although the linear regression model 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. The log cumulative exposure Cox regression model, which was the best-fitting model overall of the models investigated, yields lower EC_{01} and LEC_{01} estimates than the linear regression model of the categorical results (see Table 4-6), but the estimates based on the linear regression model are preferred because the linear regression model is more stable.

Another, more minor 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 mortality had a 15-year lag (lag periods of 0, 5, 10, 15, and 20 years were considered). A 15-year lag period means that exposures in the 15 years prior to death or the end of follow-up 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. For the best-fitting continuous model for lymphoid cancer reported by Steenland et al. (2004), the log cumulative exposure Cox regression model, the actual difference between the regression coefficients from the 15-year-lagged and the unlagged models was negligible (the regression coefficient from the unlagged model was about 8% lower than that from the 15-year-lagged model; however, it should be noted that the unlagged model did not provide a statistically significant fit to the data ($p = 0.17$) (the results for the unlagged model are presented in Section D.3.e of Appendix D).

In addition, the analyses of the NIOSH investigators indicate that the regression coefficient for cumulative exposure might have decreased with increasing follow-up, suggesting that the higher exposure levels encountered by the workers in the more distant past are having less of an impact on more recent risk. The regression coefficient for lymphoid cancers was 1.2×10^{-5} per ppm × day, for both sexes with a 10-year lag, in the 1987 follow-up (Stayner et al., 1993) versus 4.7×10^{-6} per ppm × day, for both sexes with a 15-year lag, in the 1998 follow-up (see Steenland reanalyses in Appendix D). A similar decrease was found in the regression coefficient for cumulative exposure for all lymphohematopoietic cancers. The life-table analysis used in this dose-response assessment assumes exposure accrues over the full lifetime for the cumulative exposure metric. If, in fact, exposures in the distant past cease to have a meaningful impact on the risk of lymphohematopoietic cancers, 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 follow-up 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 for lymphoid cancer yielded an LEC_{01} of 0.0156 ppm and a unit risk estimate of 0.64 per ppm, which is about 27% 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 model of the categorical results is already substantially less than that obtained

from the best-fitting log cumulative exposure Cox regression model, the estimate from the full life-table analysis is preferred. In any event, the preferred estimate is not appreciably different from the estimate from the analysis which considered only the most recent 55 years of exposure in the life-table analysis.

Several dose metrics (cumulative exposure, duration of exposure, maximum [8-hour TWA] exposure, and average exposure) were analyzed by Steenland et al. (2004), 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 the analysis, and the plants included in this cohort were specifically selected for the absence of any known confounding exposures (Stayner et al., 1993).

With respect to the breast cancer mortality response (Steenland et al., 2004), the exposure-response modeling was based on 103 deaths. As for the lymphohematopoietic cancer responses, the exposure-response data for breast cancer mortality are fairly supralinear, especially for the low-exposure groups. An attempt was again made to fit two-piece log-linear and linear spline models to the individual continuous data to address the supralinearity of the data while avoiding the extreme low-exposure curvature of the log cumulative exposure Cox regression model; however, these models resulted in low-exposure slopes that appeared to be implausibly steep and the model fits were not convincing (i.e., they were neither statistically significant nor visually compelling; see Figure 4-3). Thus, the same linear regression approach, excluding the highest exposure group, was taken to obtain a regression coefficient for the life-table analysis. As discussed above, the linear regression has its own limitations (e.g., it is based on categorical rather than continuous data and the slope is not statistically significant); nonetheless, it was judged to be the most reasonable approach for deriving low-exposure risk estimates from the available breast cancer mortality data.

For the lag period, the best-fitting model had a lag of 20 years, which was the 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, and the preferred breast cancer risk estimates are based on the breast cancer incidence data.

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 exposure-response 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). Because the subcohort with interviews had complete case ascertainment and provided data on potential confounders, it was the preferred breast cancer incidence data set, although some results based on the full cohort are presented for comparison. For the full cohort, the continuous exposure Cox regression 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 Cox regression models fit nearly equally well. For both groups, the categorical Cox regression results suggest that a linear model lying between the supralinear log cumulative exposure model and the sublinear cumulative exposure model would better represent the low-exposure data than either of the two presented continuous-variable models (see Figures 4-4 and 4-5). Thus, for both groups, in EPA's original draft analyses based on the published summary data, a linear regression was fitted to the categorical results, dropping the highest exposure group to provide a better fit to the lower-exposure data (U.S. EPA, 2006a). In addition, in subsequent analyses by Dr. Steenland (see Appendix D) of the individual data using exposure as a continuous variable, two-piece log-linear and linear spline models and other linear RR models were used to model the subcohort data; the two-piece linear spline model was the best-fitting of these models and provided the preferred breast cancer incidence risk estimates.

Confidence intervals were determined using the Wald approach. Confidence intervals for linear RR models, however, in contrast to those for the log-linear RR models, may not be symmetrical. EPA also evaluated application of a profile likelihood approach for the linear RR models (Langholz and Richardson, 2010), which allows for asymmetric CIs, for comparison with the Wald approach. Using the profile likelihood method and the two-piece linear spline model, the resulting unit risk estimate for breast cancer incidence would have been 2.33 per ppm, slightly higher (34%) than the value of 1.74 per ppm obtained as the unit risk estimate for breast cancer incidence in this assessment. These results suggest that if the profile likelihood method had been used for the linear RR models in this assessment, the total cancer risk estimate, which incorporates the breast cancer incidence estimate as a component, would be less than 34% higher than the total cancer risk estimate presented here.

With respect to the two-piece spline models, the use of this model form is not intended to imply that an abrupt change in biological response occurs at the knot but, rather, to allow description of an exposure-response relationship in which the slope of the relationship differs notably in the low-exposure versus high-exposure regions. The two-piece model is used here primarily for its representation of the low-exposure data. The main uncertainty in the two-piece spline models is in the selection of the knot, and the location of the knot is critical in defining the low-exposure slope. The model likelihood was used to provide a statistical basis for knot selection; although, as shown in Appendix D (see Figure D-1a), the likelihood did not generally change appreciably over a range of possible knots. Thus, because of the importance of knot selection, a sensitivity analysis was done to examine the impacts of selecting different knots (see Section D.6 of Appendix D). For the sensitivity analysis, the two-piece log-linear model was run with knots roughly one increment (1,000 ppm × days) below and one increment above the selected knot. For breast cancer incidence, this sensitivity analysis yielded EC_{01} estimates of 0.0133 ppm and 0.0176 ppm, respectively (i.e., about 14% lower and 14% higher, respectively, than the EC_{01} of 0.0154 ppm obtained with the originally selected knot of 6,000 ppm × days).[28]

As can be seen in Table 4-13, there is substantial variation in the EC_{01} estimates obtained from the different models. Although some plateauing is apparent with the highest exposure group and is evidenced in the subcohort with interviews by the strong influence of the top 5% of cumulative exposures on dampening the slope of the (cumulative exposure) Cox regression model (see Section D.1 and Figure D-1d of Appendix D), the categorical data for breast cancer incidence do not display the supralinearity in the lower exposure groups seen in the cases discussed above (i.e., lymphohematopoietic cancers and breast cancer mortality). Thus, for the subcohort with interviews, the difference between the EC_{01} estimates from the standard cumulative exposure Cox regression model and the two-piece spline models or the linear regression of the categorical results or continuous linear models are not as dramatic as seen in those cases (the EC_{01} estimates from the latter four approaches are nearly within an order of magnitude of that of the cumulative exposure model). For the subcohort with interviews, the two-piece spline models, the continuous linear model, and the linear regression of the categorical results gave similar results—the unit risk estimates spanned less than a fourfold range. This range is bounded by the two best-fitting (based on AIC) continuous models—the two-piece linear spline model and the continuous linear model. If the continuous linear model had been selected rather than the two-piece linear spline model, which had a slightly lower AIC value and

[28] About 12% lower and 17% higher, respectively, than the EC_{01} of 0.0151 ppm obtained with the more finely tuned knot of 5,800 ppm × days (see Appendix D). The EC_{01} value of 0.0166 presented in this assessment (see Table 4−13) is not directly comparable to the values in the sensitivity analysis because more recent background incidence and mortality rates were used in the lifetable analyses upon which the assessment estimates were based.

a better apparent visual fit of the lower-exposure data, the breast cancer incidence unit risk estimate would have been 0.446 per ppm rather than 1.74 per ppm, and the total cancer unit risk estimate would have been 1.15 per ppm rather than 2.27 per ppm. In other words, of the models investigated, the total cancer unit risk estimate from the best-fitting alternate model (based on AIC) is about 50% lower than that of the best-fitting model. However, data in the lower exposure range of greatest relevance for the derivation of a unit risk estimate support a steeper slope in the lower exposure range; thus, although the lower estimate obtained from the continuous linear model is plausible, unit risk estimates notably lower than that are considered unlikely from the available data.

The best-fitting models presented by Steenland et al. (2003) for breast cancer incidence generally had a 15-year lag (lag periods of 0, 5, 10, 15, and 20 years were considered). A 15-year lag period means that exposures in the 15 years prior to diagnosis or the end of follow-up are not taken into account. For the various continuous models for breast cancer incidence in the full cohort and the subcohort with interviews reported by Steenland et al. (2003, Tables 4 and 5), none of the unlagged models provided a statistically significant fit to the data, with the exception of the log cumulative exposure Cox regression model for the subcohort, where the unlagged model fit marginally better than the 15-year-lagged model. However, as noted in Section 4.1.2.3, 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; thus, the 15-year-lagged model was used in this assessment. The regression coefficient from the unlagged log cumulative exposure Cox regression model was about 90% higher than that from the 15-year-lagged model.

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

Regarding potential confounders/modifying factors, 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.

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 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, 2004).

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 using invasive + in situ breast cancer background rates and invasive-only background rates, using EPA's original analyses in the 2006 Draft Assessment, found that the estimate based on the invasive + in situ background rates was less than 20% higher than the corresponding estimate using only invasive breast cancer background rates (U.S. EPA, 2006a).

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. Complete interviews were available for only 68% of the 7,576 women in the full incidence cohort, and thus, some potential exists for participation selection bias in the subcohort. There is, however, no basis for considering participation to be associated with breast cancer or EtO exposure, and the major reason for nonparticipation was a failure to locate (22% of full incidence cohort) and not lack of response (3% of cohort) or refusal to participate (7% of cohort). Risk estimates based on the full cohort were calculated for comparison with the subcohort estimates using the original linear regression analyses of the categorical results. The unit risk estimate based on the subcohort was about 60% higher than the corresponding estimate from the full cohort (U.S. EPA, 2006a).

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 available). Second, these occupational epidemiology data represent a healthy-worker cohort. Third, the epidemiologic study may not have sufficient statistical power and follow-up time to observe associations for all the tumor sites that may be affected by EtO.

The first limitation was addressed quantitatively in the life-table analysis for the 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 incidence unit risk estimate is about 120% higher than (i.e., 2.2 times) the mortality-based estimate, which seems reasonable given the relatively high survival rates for lymphoid cancers (according to SEER data [www.seer.cancer.gov], 5-year survival rates are 65% for NHL; 78% for chronic lymphocytic leukemia, which are the vast majority of the lymphocytic leukemias in adults; and 40% for multiple myeloma).

The healthy-worker effect is often an issue in occupational epidemiology studies, but the internal exposure-response analyses conducted by these investigators help address this concern, at least partially. In terms of representing the general population, the NIOSH study cohort was relatively diverse. It contained both female (55%) and male workers, and the workers were 79% white, 16% black, and 5% "other." Furthermore, because of EtO's mutagenic mode of action, increased early-life susceptibility is assumed and ADAFs are applied for exposure scenarios involving early life (see Section 4.4).

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

To obtain the risk estimate for total cancer risk (2.3 per ppm, or 2.3×10^{-3} per ppb), the preferred estimates for lymphoid cancer incidence and breast cancer incidence were combined. While there are uncertainties in the approach used to combine the individual estimates, the resulting unit risk estimate is appropriately bounded in the roughly twofold range between estimates based on the sum of the individual MLEs of risk and the sum of the individual 95% UCLs, and thus, any inaccuracy in the total cancer unit risk estimate resulting from the approach used is relatively minor. Because the breast cancer component of the total cancer risk estimate applies only to females, the total cancer risk estimate is expected to overestimate the cancer risk to males somewhat (the preferred unit risk estimate for lymphoid cancer alone was 0.877 per ppm [or 8.77×10^{-4} per ppb], which is about 40% of the total cancer risk estimate).

Despite these uncertainties, the inhalation cancer unit risk estimate of 2.3 per ppm (or 2.3×10^{-3} per ppb) for the total cancer risk from lymphoid cancer incidence and female breast cancer incidence has the advantages of being based on human data from a large, high-quality epidemiologic study with individual exposure estimates for each worker. Furthermore, the breast cancer component of the risk estimate, which contributes approximately 60% of the total cancer risk, is based on a substantial number of incident cases (233 total, the vast majority of which

were in the exposure range below the knot of 5,800 ppm × days [see Table D.1a of Appendix D]).

A further area of uncertainty pertains to the assumption that RR is independent of age, which is a common assumption in the dose-response modeling of epidemiological data and is an underlying assumption in the Cox regression model. For the NIOSH worker cohort, the proportional hazards model assumption of RR being independent of age was tested by checking the significance of an interaction between age and cumulative exposure, and none of the models had a significant interaction term. This suggests that, for adults at least, the assumption that RR is independent of age is valid. However, the worker cohort contains no children and is uninformative on the issue of early-life susceptibility. In the absence of data on early-life susceptibility, EPA's *Supplemental Guidance* (U.S. EPA, 2005b) recommends that increased early-life susceptibility be assumed for carcinogens with a mutagenic mode of action, and the conclusion was made in Section 3.4 that the weight of evidence supports a mutagenic mode of action for EtO. Thus, in accordance with the *Supplemental Guidance*, the alternate assumption of increased early-life susceptibility is preferred as the basis for risk estimates in this assessment, and risk estimates derived under this preferred assumption are presented in Section 4.4.

4.1.5. Summary

Under the common assumption that RR is independent of age, an inhalation unit risk estimate for lymphoid cancer incidence of 0.877 per ppm (or 8.77×10^{-4} per ppb; 4.79×10^{-4} per $\mu g/m^3$) was calculated using a life-table analysis and a weighted linear regression of the categorical Cox regression results, excluding the highest exposure group, for excess lymphoid cancer mortality from a high-quality occupational epidemiology study. Similarly, an inhalation unit risk estimate for female breast cancer incidence of 1.74 per ppm (or 1.74×10^{-3} per ppb; 9.51×10^{-4} per $\mu g/m^3$) was calculated using a life-table analysis and two-piece linear spline modeling of the continuous data for excess breast cancer incidence from the same high-quality occupational epidemiology study. The linear regression of the categorical results with the exclusion of the highest exposure group for the lymphoid cancer results and the two-piece linear spline analysis for the breast cancer incidence data were different modeling approaches used to address the supralinearity of the exposure-response data in the two data sets. Low-dose linear extrapolation was used, as warranted by the clear mutagenicity of EtO. An EC_{01} estimate of 0.0078 ppm, a LEC_{01} estimate of 0.0044 ppm, and a unit risk estimate of 2.3 per ppm (or 2.3×10^{-3} per ppb; 1.2×10^{-3} per $\mu g/m^3$) were obtained for the total cancer risk combined across both cancer types. Despite the uncertainties discussed above, this inhalation unit risk estimate

has the advantages of being based on human data from a high-quality epidemiologic study with individual exposure estimates for each worker.

In the absence of data on early-life susceptibility, EPA's *Supplemental Guidance* (U.S. EPA, 2005a) recommends that increased early-life susceptibility be assumed for carcinogens with a mutagenic mode of action, and the conclusion was made in Section 3.4 that the weight of evidence supports a mutagenic mode of action for EtO. Thus, in accordance with the *Supplemental Guidance*, the alternate assumption of increased early-life susceptibility is preferred as the basis for risk estimates in this assessment, and risk estimates derived under this preferred assumption are presented in Section 4.4. Other than the use of the alternate assumption about early-life susceptibility, the approach used to derive the estimates presented in Section 4.4 is identical to the approach used for the estimates derived here in Section 4.1, and the comparisons made between various options and the issues and uncertainties discussed here in Section 4.1 are applicable to the estimates derived in Section 4.4.

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 3-3 through 3-5. These studies have also been reviewed by the IARC (1994b) 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 3-3 through 3-5.

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 3-2). This modeling was validated against measured blood EtO concentrations for rodents and humans. 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:

$$RGDR_{PU} = (RGD_{PU})_m/(RGD_{PU})_h = (Q_{alv}/SA_{PU})_m/(Q_{alv}/SA_{PU})h, \quad (4\text{-}4)$$

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),

$$RGDR_{PU} = ((0.78\ L/h)/(0.05\ m^2))/((255\ L/h)/(54.0\ m^2)) = 3.3. \quad (4\text{-}5)$$

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 the following steps were used:

1. *Extract the incidence data presented in the original studies.* In order to crudely adjust for early mortality in the analysis of the NTP (1987) data, the incidence data have been corrected

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 3-3 through 3-5 match the original 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 G.

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:

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k) \times (t - t_0)^z], \quad (4\text{-}6)$$

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 3-3 through 3-5 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 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:

$$95\%\ UCL = MLE + 1.645(SE), \qquad (4\text{-}7)$$

where SE 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 4-16.

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

Table 4-16. Upper-bound unit risks (per µg/m^3) obtained by combining tumor sites

Combination method[a]	NTP (1987) female mouse	Lynch et al. (1984a); Lynch et al. (1984b) male rat	Snellings et al. (1984)[b]	
			Male rat	Female rat
UCL 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 3-3.
[c]UCL = 95% upper confidence bound. At a given dose, the 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 3-1 through 3-3.

adenocarcinomas, and mammary carcinomas were found in females. These data are shown in Table 3-3.

Lynch et al. [Lynch et al. (1984a); Lynch et al. (1984b)] 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 3-4, 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. (1986, 1985) described the development of brain tumors in a different set of F344 rats. The Snellings et al. (1984) 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 incidences in the animals killed after 24 months in Snellings et al.

(1984) are shown in Table 3-5. Table 3-5 also presents the brain tumor incidence data for male and female rats from the Garman et al. (1986, 1985) publications. The brain tumor incidence was lower than that of the other tumors, particularly the splenic mononuclear cell leukemias.

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 3-3 through 3-5. The highest unit risk of any individual site is 3.23×10^{-5} per $\mu g/m^3$, which is for mononuclear cell leukemia in the female rats of the Snellings et al. (1984) study.

Table 4-17 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 3-3. 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 4-17. 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. (1984a); Lynch et al. (1984b) 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 4-16. The sums of the individual unit risks tabulated in Tables 3-3 to 3-5 are given in the second row of Table 4-16. 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. [Lynch et al. (1984a); Lynch et al. (1984b)] 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 zero extra risk at zero 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

Table 4-17. 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 μg/m^3) from time-to-tumor analysis	Unit risk, 0.1/LEC_{10} (per μg/m^3) (Table 3-3)[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]$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k) \times (t - t_0)^z]$, 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.

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 because it avoids the overestimate. However, for the exceptional Lynch et al. [Lynch et al. (1984a); Lynch et al. (1984b)] data, the sum of upper bounds, 3.66×10^{-5} per μg/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 μg/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 4-18. For the Snellings et al. (1984) data sets, the upper confidence bound on the sum of risks is used in the summary Table 4-18. The results of the sum-of-risks calculations on the NTP bioassay time-to-tumor data are included in the third row of Table 4-16. The estimate for the NTP female mice is 4.55×10^{-5} per μg/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 4-18. The data set giving the highest risk (4.55×10^{-5} per μg/m^3) is the NTP (1987) data

Table 4-18. 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. (1984a); Lynch et al. (1984b), 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 4-17.
[b]Upper bound on sum of risks from the time-to-tumor analysis of the NTP data, Table 4-16.
[c]Sum of (upper bound) unit risks (see text for explanation), Table 4-16.
[d]Upper bound on sum of risks, Table 4-16.

on combined tumors in female mice. The other values are within about a factor of 2 of the highest value.

4.3. SUMMARY OF INHALATION UNIT RISK ESTIMATES—NOT ACCOUNTING FOR ASSUMED INCREASED EARLY-LIFE SUSCEPTIBILITY

For both humans and laboratory animals, tumors occur at multiple sites. In humans, there was a combination of tumors having lymphohematopoietic, in particular lymphoid, origins in both sexes and breast cancer in females, and, in rodents, lymphohematopoietic tumors, mammary carcinomas, and tumors of other sites were observed. From human data, an extra cancer unit risk estimate of 4.79×10^{-4} per μg/m^3 (8.77×10^{-4} per ppb) was calculated for lymphoid cancer incidence, and a unit risk estimate of 9.31×10^{-4} per μg/m^3 (1.74×10^{-3} per ppb) was calculated for breast cancer incidence in females. The total extra cancer unit risk estimate was 1.2×10^{-3} per μg/m^3 (2.3×10^{-3} per ppb) for both cancer types combined (EC_{01} = 0.0078 ppm; LEC_{01} = 0.0043 ppm). Unit risk estimates derived from the three chronic rodent bioassays for EtO ranged from 2.2×10^{-5} per μg/m^3 to 4.6×10^{-5} per μg/m^3, over an order of magnitude lower than the estimates based on human data.

Adequate human data, if available, are considered to provide a more appropriate basis than 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 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 total extra cancer unit risk estimate of 1.2×10^{-3} per μg/m^3 (2.3×10^{-3} per ppb) calculated for lymphoid cancers and breast cancer combined is the preferred estimate of those estimates not taking assumed increased early-

life susceptibility into account (estimates accounting for assumed increased early-life susceptibility are presented in Section 4.4). The unit risk estimate is intended to be an upper bound on cancer risk for use with exposures below the POD (i.e., the LEC_{01}). The unit risk estimate should not generally be used above the POD; however, in the case of this total extra cancer unit risk, which is based on cancer type-specific unit risk estimates from two linear models, the estimate should be valid for exposures up to about 0.075 ppm (140 $\mu g/m^3$), which is the minimum of the limits for the lymphoid cancer unit risk estimate (0.090 ppm; see Section 4.1.1.2) and the breast cancer unit risk estimate (0.075 ppm; see Section 4.1.2.3).

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; see Section 4.4 below for more details on the application of ADAFs).

4.4. ADJUSTMENTS FOR POTENTIAL INCREASED EARLY-LIFE SUSCEPTIBILITY

There are no chemical-specific data on age-specific susceptibility to EtO-induced carcinogenesis. However, there is sufficient weight of evidence to conclude that EtO operates through a mutagenic mode of action (see Section 3.4.1). In such circumstances (i.e., the absence of chemical-specific data on age-specific susceptibility but sufficient evidence of a mutagenic mode of action), EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b) recommends the assumption of increased early-life susceptibility and the application of default age-dependent adjustment factors (ADAFs) to adjust for this potential increased susceptibility from early-life exposure. See the *Supplemental Guidance* for detailed information on the general application of these adjustment factors. In brief, the *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). For risk assessments based on specific exposure assessments, the 10-fold and 3-fold adjustments to the unit risk estimates are to be combined with age-specific exposure estimates when estimating cancer risks from early-life (<16 years of age) exposure.

These ADAFs, however, were formulated based on comparisons of the ratios of cancer potency estimates from juvenile-only exposures to cancer potency estimates from adult-only exposures from rodent bioassay data sets with appropriate exposure scenarios, and they are

designed to be applied to cancer potency estimates derived from adult-only exposures. Thus, alternate life-table analyses were conducted to derive comparable adult-exposure-only unit risk estimates to which ADAFs would be applied to account for early-life exposure. For these alternate life-table analyses, it was assumed that RR is independent of age for adults, which represent the life stage for which the exposure-response data and the Cox regression modeling results from the NIOSH cohort study specifically pertain, but that there is increased early-life susceptibility, based on the weight-of-evidence-based conclusion that EtO carcinogenicity has a mutagenic mode of action (see Section 3.4), which supersedes the assumption that RR is independent of age for all ages including children.

In the alternate analyses, exposure in the life table was taken to start at age 16 years, the age cut point that was established in EPA's *Supplemental Guidance* (U.S. EPA, 2005b), to derive an adult-exposure-only unit risk estimate to which ADAFs would be applied to account for early-life exposure. Other than the age at which exposure was initiated, the life-table analyses are identical to those conducted for the results presented in Section 4.1. Adult-exposure-only unit risk estimates were derived for both cancer incidence and mortality for both lymphoid and breast cancers. Alternate estimates were not derived for all lymphohematopoietic cancers because lymphoid cancer was the preferred endpoint (see Section 4.1.1.2). Incidence estimates are preferred over mortality estimates, but both are calculated here for comparison and because mortality estimates are sometimes used in addition to incidence estimates in benefit-cost analyses. For each cancer endpoint, the same exposure-response model was used as that which was selected for the unit risk estimates in Section 4.1 (i.e., linear regression of the categorical results, excluding the highest exposure category, for lymphoid cancer and breast cancer mortality and two-piece linear spline model for breast cancer incidence). The results are presented in Table 4-19 along with the unit risk estimates derived assuming that RR was independent of age for all ages (see Section 4.1) for comparison. As can be seen in Table 4-19, the unit risk estimates for adult-only exposures range from about 66% to about 72% of the unit risk estimates derived under the assumption of age independence across all ages.

According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) cancer risk estimates are intended to reflect total cancer risk, not site-specific cancer risk; therefore, an additional calculation was made to estimate the combined risk for (incident) lymphoid and breast cancers from adult-only exposures, because females would be at risk for both cancer types. Assuming that the tumor types are independent and that the risk estimates are approximately normally distributed, this calculation can be made as described in Section 4.1.3. First, an EC_{01} of 0.0114 ppm for the total cancer risk (i.e., lymphoid cancer incidence + breast cancer incidence) from adult-only exposure was estimated, as summarized in Table 4-20.

Table 4-19. EC_{01}, LEC_{01}, and unit risk estimates for adult-only exposures*

Cancer response	EC_{01} (ppm)	LEC_{01} (ppm)	Adult-exposure-only unit risk estimate[a] (per ppm)	Lifetime-exposure unit risk estimate under assumption of age independence[b] (per ppm)
Lymphoid cancer mortality (both sexes)	0.0787	0.0352	0.284	0.397
Lymphoid cancer incidence (both sexes)	0.0364	0.0163	0.613	0.877
Breast cancer mortality (females)	0.0590	0.0297	0.337	0.513
Breast cancer incidence (females)	0.0167	0.00863	1.16[c]	1.74[c]

[a]Unit risk estimate = $0.01/LEC_{01}$.
[b]From Tables 4–5, 4–9, and 4–13 of Section 4.1.
[c]For unit risk estimates above 1, convert to risk per ppb (e.g., 1.16 per ppm = 1.16×10^{-3} per ppb).
*These are intermediate values. See Table 4-22 below for the final adult-based cancer-type-specific unit risk estimates.

Table 4-20. Calculation of EC_{01} for total cancer risk from adult-only exposure

Cancer type	EC_{01} (ppm)	$0.01/EC_{01}$ (per ppm)	EC_{01} for total risk (ppm)
Lymphoid	0.0364	0.275	--
Breast	0.0167	0.599	--
Total[a]	--	0.874	0.0114

[a]The total $0.01/EC_{01}$ value equals the sum of the individual $0.01/EC_{01}$ values; the EC_{01} for the total cancer risk then equals $0.01/(0.01/EC_{01})$.

Then, a unit risk estimate of 1.5 per ppm for the total cancer risk (i.e., lymphoid cancer incidence + breast cancer incidence) from adult-only exposure was derived, as shown in Table 4−21. An LEC_{01} estimate of 0.00654 ppm for the total cancer risk can be calculated as 0.01/(1.53 per ppm).

Thus, the total cancer unit risk estimate from adult-only exposure is 1.53 per ppm (or 1.53×10^{-3} per ppb; 8.36×10^{-4} per μg/m^3). While there are uncertainties regarding the assumption of a normal distribution of risk estimates, the resulting unit risk estimate is appropriately bounded in the roughly twofold range between estimates based on the sum of the

Table 4-21. Calculation of total cancer unit risk estimate from adult-only exposure*

Cancer type	Adult-exposure-only unit risk estimate (per ppm)	$0.01/EC_{01}$ (per ppm)	SE[a] (per ppm)	Variance	Adult-exposure-only total cancer unit risk estimate (per ppm)
Lymphoid	0.613	0.275	0.205	0.0422	--
Breast	1.16	0.599	0.340	0.115	--
Total	--	0.874	(0.397)[b]	0.158	1.53[c]

*These are intermediate values. See Table 4-22 below for the final adult-based cancer-type-specific unit risk estimates.

[a]SE = (unit risk – $0.01/EC_{01}$)/1.645.

[b]The SE of the total cancer risk is calculated as the square root of the sum of the variances (next column), not as the sum of the SEs.

[c]Total cancer unit risk = 0.874 + 1.645 × 0.397.

individual MLEs (i.e., 0.874) and the sum of the individual 95% UCLs (i.e., unit risk estimates, 1.77), or more precisely in this case, between the largest individual unit risk estimate (1.16) and the sum of the unit risk estimates (1.77), and thus, any inaccuracy in the total cancer risk estimate resulting from the approach used to combine risk estimates across cancer types is relatively minor.

When EPA derives unit risk estimates from rodent bioassay data, there is a blurring of the distinction between lifetime and adult-only exposures because the relative amount of time that a rodent spends as a juvenile is negligible (<8%) compared to its lifespan. [According to EPA's *Supplemental Guidance*, puberty begins around 5−7 weeks of age in rats and around 4−6 weeks in mice (U.S. EPA, 2005b)]. Thus, when exposure in a rodent is initiated at 5–8 weeks, as in the typical rodent bioassay, and the bioassay is terminated after 104 weeks of exposure, the unit risk estimate derived from the resulting cancer incidence data is considered a unit risk estimate from lifetime exposure, except when the ADAFs were formulated and are applied, in which case the same estimate is considered to apply to adult-only exposure. Yet, when adult exposures are considered in the application of ADAFs, the adult-exposure-only unit risk estimate is pro-rated over the full default human lifespan of 70 years, presumably because that is how adult exposures are treated when a unit risk estimate calculated in the same manner from the same bioassay exposure paradigm is taken as a lifetime unit risk estimate.

However, in humans, a greater proportion of time is spent in childhood (e.g., 16 of 70 years = 23%), and the distinction between lifetime exposure and adult-only exposure cannot be ignored when human data are used as the basis for the unit risk estimates. Thus, as described

above, adult-exposure-only unit risk estimates were calculated distinct from the lifetime estimates that were derived in Section 4.1 under the assumption of age independence for all ages. In addition, the adult-exposure-only unit risk estimates need to be rescaled to a 70-year lifespan in order to be used in the ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios in the standard manner, which includes prorating even adult-based unit risk estimates over 70 years. Thus, the adult-exposure-only unit risk estimates are multiplied by 70/54 to rescale the 54-year adult period of the 70-year default lifespan to 70 years. Then, for example, if a risk estimate were calculated for a less-than-lifetime exposure scenario involving exposure only for the full adult period of 54 years, the rescaled unit risk estimate would be multiplied by 54/70 in the standard calculation and the adult-exposure-only unit risk estimate would be appropriately reproduced. Without rescaling the adult-exposure-only unit risk estimates, the example calculation just described for exposure only for the full adult period of 54 years would result in a risk estimate 77% (i.e., 54/70) of that obtained directly from the adult-exposure-only unit risk estimates, which would be illogical. The rescaled adult-based unit risk estimates for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios are presented in Table 4-22. Rescaled LEC_{01} and EC_{01} estimates for adult-based total cancer risk are 5.0×10^{-3} ppm (9.2 μg/m^3) and 8.8×10^{-3} ppm (16 μg/m^3).

Table 4-22. Adult-based unit risk estimates for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios

Cancer response	Adult-based unit risk estimate (per ppm)	Adult-based unit risk estimate (per μg/m^3)
Lymphoid cancer mortality	0.368	2.01×10^{-4}
Lymphoid cancer incidence	0.795	4.35×10^{-4}
Breast cancer mortality	0.436	2.39×10^{-4}
Breast cancer incidence	1.50[a]	8.21×10^{-4}
Total cancer incidence	1.98[a]	1.08×10^{-3}

[a]For unit risk estimates above 1, convert to risk per ppb (e.g., 1.16 per ppm = 1.16×10^{-3} per ppb).

An example calculation illustrating the application of the ADAFs to the human-data-derived adult-based (rescaled as discussed above) unit risk estimate for EtO for a lifetime exposure scenario is presented below. For inhalation exposures, assuming ppm equivalence across age groups, i.e., equivalent risk from equivalent exposure levels, independent of body

size, the ADAF calculation is fairly straightforward. Thus, the ADAF-adjusted lifetime total-cancer unit risk estimate is calculated as follows:

total cancer risk from exposure to constant EtO exposure level of 1 μg/m^3 from ages 0–70 years:

Age group	ADAF	unit risk (per μg/m^3)	exposure conc (μg/m^3)	duration adjustment	partial risk
0 to <2 years	10	1.08×10^{-3}	1	2 years/70 years	3.09×10^{-4}
2 to <16 years	3	1.08×10^{-3}	1	14 years/70 years	6.48×10^{-4}
≥16 years	1	1.08×10^{-3}	1	54 years/70 years	8.33×10^{-4}
				total lifetime risk =	1.80×10^{-3}

The partial risk for each age group is the product of the values in columns 2–5 [e.g., $10 \times (1.08 \times 10^{-3}) \times 1 \times 2/70 = 3.09 \times 10^{-4}$], and the total risk is the sum of the partial risks.

This 70-year risk estimate for a constant exposure of 1 μg/m^3 is equivalent to a **lifetime unit risk estimate of 1.8×10^{-3} per μg/m^3** (3.3 per ppm, or 3.3×10^{-3} per ppb), adjusted for potential increased early-life susceptibility, assuming a 70-year lifetime and constant exposure across age groups. Note that because of the use of the rescaled adult-based unit risk estimate, the partial risk for the ≥16 years age group is the same as would be obtained for a 1 μg/m^3 constant exposure directly from the total cancer adult-exposure-only unit risk estimate of 8.36×10^{-4} per μg/m^3 that was presented above, as it should be (the small difference in the second decimal place is due to round-off error).

In addition to the uncertainties discussed above for the inhalation unit risk estimate, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The ADAFs reflect an expectation of increased risk from early-life exposure to carcinogens with a mutagenic mode of action (U.S. EPA, 2005b), but they are general adjustment factors and are not specific to EtO. With respect to the breast cancer estimates, for example, evidence suggests that puberty/early adulthood is a particularly susceptible life stage for breast cancer induction (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.

4.5. 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, in particular lymphoid, origins in

both sexes and breast cancer in females, and, in rodents, lymphohematopoietic tumors, mammary carcinomas, and tumors of other sites were observed. From human data, an extra cancer unit risk estimate of 4.79×10^{-4} per $\mu g/m^3$ (8.77×10^{-4} per ppb) was calculated for lymphoid cancer incidence, and a unit risk estimate of 9.49×10^{-4} per $\mu g/m^3$ (1.74×10^{-3} per ppb) was calculated for breast cancer incidence in females, under the assumption that RR is independent of age for all ages (see Section 4.1). The total extra cancer unit risk estimate was 1.24×10^{-3} per $\mu g/m^3$ (2.27×10^{-3} per ppb) for both cancer types combined (EC_{01} = 0.00775 ppm; LEC_{01} = 0.00441 ppm). 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 $\mu g/m^3$, over an order of magnitude lower than the estimates based on human data.

Because a mutagenic mode of action for EtO carcinogenicity (see Section 3.4.1) 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, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b). This assumption of increased early-life susceptibility supersedes the assumption of age independence under which the human-data-based estimates presented in the previous paragraph were derived. Thus, as described in Section 4.4, adult-exposure-only unit risk estimates were calculated from the human data under an alternate assumption that RR is independent of age for adults, which represent the life stage for which the data upon which the exposure-response modeling was conducted pertain. These adult-exposure-only unit risk estimates were then rescaled to a 70-year basis for use in the standard ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios. The resulting adult-based unit risk estimates were 4.35×10^{-4} per $\mu g/m^3$ (7.95×10^{-4} per ppb) for lymphoid cancer incidence and 8.21×10^{-4} per $\mu g/m^3$ (1.50×10^{-3} per ppb) for breast cancer incidence in females. The adult-based total extra cancer unit risk estimate for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios was 1.08×10^{-3} per $\mu g/m^3$ (1.98×10^{-3} per ppb) for both cancer types combined.

For exposure scenarios involving early-life exposure, the age-dependent adjustment factors (ADAFs) should be applied, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b). Applying the ADAFs to obtain a full lifetime unit risk estimate yields

$$1.98/\text{ppm} \times ((10 \times 2 \text{ years}/70 \text{ years}) + (3 \times 14/70) + (1 \times 54/70)) \quad (4\text{-}8)$$
$$= 3.29/\text{ppm} = 1.80 \times 10^{-3}/(\mu g/m^3).$$

Applying the ADAFs to the unit risk estimates derived from the three chronic rodent bioassays for EtO yields estimates ranging from 3.7×10^{-5} per $\mu g/m^3$ to 7.6×10^{-5} per $\mu g/m^3$, still over an order of magnitude lower than the estimate based on human data.

Adequate human data, if available, are considered to provide a more appropriate basis than 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 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 human-based **full lifetime total extra cancer unit risk estimate of 1.8×10^{-3} per $\mu g/m^3$ (3.3×10^{-3} per ppb)** calculated for lymphoid cancers and breast cancer combined and applying the ADAFs is the preferred lifetime unit risk estimate. For less-than-lifetime exposure scenarios, the human-data-derived (rescaled) adult-based unit risk estimate of 1.1×10^{-3} per $\mu g/m^3$ (2.0×10^{-3} per ppb) should be used, in conjunction with the ADAFs if early-life exposures occur.

Although there are uncertainties in this unit risk estimate, primarily related to exposure misclassification, model uncertainty, and low-dose extrapolation, as discussed in Section 4.1.4, confidence in the unit risk estimate is relatively high. First, there is strong confidence in the hazard characterization of EtO as "carcinogenic to humans," which is based on strong epidemiological evidence supplemented by other lines of evidence, such as genotoxicity in both rodents and humans (see Section 3.5.1). Second, the unit risk estimate is based on human data from a large, high-quality epidemiology study with individual worker exposures estimated using a high-quality regression model (see Section 4.1 and Section A.2.8 of Appendix A). Finally, the use of low-exposure linear extrapolation is strongly supported by the conclusion that EtO carcinogenicity has a mutagenic mode of action (see Section 3.4.1).

Confidence in the unit risk estimate is particularly high for the breast cancer component, the largest contributor to the total cancer unit risk estimate, which is based on over 200 incident cases for which the investigators had information on other potential breast cancer risk factors (see Section 4.1.2.3). The selected model for the breast cancer incidence data was the best-fitting model of the models investigated as well as the model that provided the best representation of the categorical results, particularly in the lower exposure range of greatest relevance for the derivation of a unit risk estimate. Alternate estimates calculated from other reasonable models suggest that a unit risk estimate for breast cancer incidence that is fourfold lower (corresponding to a total cancer unit risk estimate of twofold lower) is plausible; however, unit risk estimates notably lower than that are considered unlikely from the available data.

There is lower confidence in the lymphoid cancer component of the unit risk estimate because it is based on fewer events (40 lymphoid cancer deaths); incidence risk was estimated from mortality data; and the exposure-response relationship is exceedingly supralinear, such that continuous models yield apparently implausibly steep low-exposure slopes (see Figure 4-1). Although these continuous models provided statistically significant slope coefficients, there was low confidence in such steep slopes, which, particularly for the two-piece spline models, are highly dependent on a small number of cases in the low-exposure range. Thus, a linear regression model of the categorical results for the lowest three quartiles was used to derive the unit risk estimate for lymphoid cancer, and there was greater confidence in the more moderate slope resulting from that model, although it was not statistically significant, because it was based on more data and provided a good representation of the categorical results across this larger data range in the lower-exposure region (see Section 4.1.1.2). So, while there is lower confidence in the lymphoid cancer unit risk estimate than in the breast cancer unit risk estimate, the lymphoid cancer estimate is considered a reasonable estimate from the available data, and overall, there is relatively high confidence in the total cancer unit risk estimate.

The unit risk estimate is intended to be an upper bound on cancer risk for use with exposures below the POD (i.e., the LEC_{01}). The unit risk estimate should not generally be used above the POD; however, in the case of this total extra cancer unit risk, which is based on cancer type-specific unit risk estimates from two linear models, the estimate should be valid for exposures up to about 0.075 ppm (140 $\mu g/m^3$), which is the minimum of the limits for the lymphoid cancer unit risk estimate (0.090 ppm: see Section 4.1.1.2) and the breast cancer unit risk estimate (0.075 ppm; see Section 4.1.2.3). (See Section 4.7 for risk estimates based on occupational exposure scenarios.)

Using the above full lifetime unit risk estimate of 3.3×10^{-3} per ppb (1.8×10^{-3} per $\mu g/m^3$), the lifetime chronic exposure level of EtO corresponding to an increased cancer risk of 10^{-6} can be estimated as follows:

$$(10^{-6})/(3.3/\text{ppm}) = 3.0 \times 10^{-7} \text{ ppm} = 0.00030 \text{ ppb} = 0.0006 \ \mu g/m^3. \quad (4\text{-}9)$$

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, estimates of "central tendency" for the risk below the POD are also presented. Adult-based extra risk estimates per ppm for some of the cancer responses, based on linear extrapolation from the adult-exposure-only EC_{01} (i.e., $0.01/EC_{01}$) and rescaling to a

70-year basis for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios (see Section 4.4), are reported in Table 4-23. The adult-exposure-only EC_{01}s were from the linear regression models of the categorical results for lymphoid cancers and breast cancer mortality and from the two-piece linear spline model (low-dose segment) for breast cancer incidence. (Note that, for each of these models, the low-exposure extrapolated estimates are a straight linear continuation of the linear models used above the PODs, and thus, the statistical properties of the models are preserved.) These estimates are dependent on the suitability of the EC_{01} estimates as well as on the applicability of the linear low-dose extrapolation. The assumption of low-dose linearity is supported by the mutagenicity of EtO (see Section 3.4). If these estimates are to be used, ADAFs should be applied if early-life exposure occurs, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b).

As can be seen by comparing the adult-based rescaled $0.01/EC_{01}$estimates in Table 4-23 with the adult-based unit risk estimates in Table 4-22, the $0.01/EC_{01}$ estimates are about 45% of the unit risk estimates for the lymphoid cancer responses and about 50% of the unit risk estimates for the breast cancer responses.

Table 4-23. Adult-based extra risk estimates per ppm based on adult-exposure-only EC_{01}s[a]

Cancer response	EC_{01} (ppm)	Adult-based $0.01/EC_{01}$ (per ppm)[b]
Lymphoid cancer mortality (both sexes)	0.0787	0.165
Lymphoid cancer incidence (both sexes)	0.0364	0.356
Breast cancer mortality (females)	0.0590	0.219
Breast cancer incidence (females)	0.0167	0.776
Total cancer incidence	0.0114	1.14[c]

[a]ADAFs should be applied if early-life exposure occurs, in accordance with EPA's *Supplemental Guidance*.
[b]These estimates are calculated as $0.01/EC_{01}$ for the adult-exposure-only extra risk estimate per ppm rescaled to a 70-yr basis by multiplying by 70/54 (see Section 4.4).
[c]For unit risk estimates above 1, convert to risk per ppb (e.g., 1.14 per ppm = 1.14×10^{-3} per ppb).

Finally, it should be noted that some investigators have posited that the high and variable background levels of endogenous EtO-induced DNA damage in the body (see Section 3.3.3.1) may overwhelm any contribution from low levels of exogenous EtO exposure (Marsden et al., 2009; SAB, 2007). It is true that the existence of these high and variable background levels may

make it hard to observe statistically significant increases in risk from low levels of exogenous exposure. However, there is clear evidence of carcinogenic hazard from the rodent bioassays and strong evidence from human studies (see Section 3.5), and the genotoxicity/mutagenicity of EtO (see Section 3.4) supports low-dose linear extrapolation of risk estimates from those studies (U.S. EPA, 2005a). In fact, as noted in Section 3.3.3.1, Marsden et al. (2009), using sensitive detection techniques and an approach designed to separately quantify both endogenous N7-HEG adducts and "exogenous" N7-HEG adducts induced by EtO treatment in rats, reported increases in exogenous adducts in DNA of spleen and liver consistent with a linear dose-response relationship ($p < 0.05$), down to the lowest dose administered (0.0001 mg/kg injected i.p. daily for 3 days, which is a very low dose compared to the LOAELs in the carcinogenicity bioassays; see Section C.7 of Appendix C). Furthermore, while the contributions to DNA damage from low exogenous EtO exposures may be relatively small compared to those from endogenous EtO exposure, low levels of exogenous EtO may nonetheless be responsible for levels of risk (above background risk). This is not inconsistent with the much higher levels of background cancer risk, to which endogenous EtO may contribute, for the two cancer types observed in the human studies—lymphoid cancers have a background lifetime incidence risk on the order of 3%, while the background lifetime incidence risk for breast cancer is on the order of 15%.[29]

See Table 4-24 for a summary of key unit risk estimates derived in this assessment. See Section 4.7 for risk estimates based on occupational exposure scenarios.

4.6. COMPARISON WITH OTHER PUBLISHED RISK ESTIMATES

The unit risk values derived in this document are compared with other recent risk estimates presented in the published literature (see Table 4-25).

4.6.1. Unit Risk Estimates Based on Human Studies

Kirman et al. (2004) used leukemia data only and pooled data from both the Stayner et al. (1993) and the UCC studies (Teta et al., 1999; Teta et al., 1993). Based on the assumption that leukemias are due to chromosome translocations, requiring two independent events (chromosome breaks), the Kirman et al. (2004) proposed that two independent EtO-induced events are required for EtO-induced leukemias and used a dose-squared model, yielding a unit risk value of 4.5×10^{-8} $(\mu g/m^3)^{-1}$ as their preferred estimate.

[29]These background lifetime incidence values were obtained from the lifetable analysis, based on SEER rates, as discussed in Sections 4.1.1.3 and 4.1.2.3. For lymphoid cancer, for example, see the value of Ro at the bottom of the lifetable analysis in Appendix E.

Table 4-24. Summary of key unit risk estimates from this assessment (see Section 4.7 for risk estimates based on occupational exposure scenarios)

Basis	Inhalation unit risk estimate[a] (per µg/m^3)[b]
Full lifetime unit risk estimate[c]	
Total cancer risk based on human data (NIOSH cohort of sterilizer workers)—lymphoid cancer incidence (linear regression of categorical results) and breast cancer incidence in females (2-piece linear spline model)	**1.80×10^{-3}**
Adult-based unit risk estimates[d]	
Total cancer risk based on human data (NIOSH cohort)—lymphoid cancer incidence (linear regression of categorical results) and breast cancer incidence in females (2-piece linear spline model)	**1.08×10^{-3}**
Lymphoid cancer incidence based on human data (NIOSH)—linear regression of categorical results	4.35×10^{-4}
Breast cancer incidence in females based on human data (NIOSH)—stimate based on best-fitting model: the 2-piece linear spline model	8.21×10^{-4}
Breast cancer incidence in females based on human data (NIOSH)—range based on 3 reasonable statistically significant continuous models: 2-piece linear spline model, 2-piece log-linear spline model, and linear model	2.10×10^{-4} to 8.21×10^{-4}
Total cancer risk based on human data (NIOSH cohort)—lymphoid cancer incidence (linear regression of categorical results) and range of female breast cancer incidence estimates (2-piece linear spline model, 2-piece log-linear spline model, and linear model)	5.64×10^{-4} to 1.08×10^{-3}
Lymphoid cancer mortality based on human data (NIOSH)—linear regression of categorical results	2.01×10^{-4}
Breast cancer mortality in females based on human data (NIOSH)—linear regression of categorical results	2.39×10^{-4}
Preferred total cancer incidence risk estimate from rodent data (female mouse)	4.6×10^{-5}
Range of total cancer incidence risk estimates from rodent data (mouse and rat)	2.2×10^{-5} to 4.6×10^{-5}
0.01/EC_{01}estimates[e]	
Lymphoid cancer incidence based on human data (NIOSH)—linear regression of categorical results	1.9×10^{-4}
Breast cancer incidence in females based on human data (NIOSH)—estimate based on best-fitting model: the 2-piece linear spline model	4.2×10^{-4}
Lymphoid cancer mortality based on human data (NIOSH)—linear regression of categorical results	9.0×10^{-5}

Table 4 24. Summary of key unit risk estimates from this assessment (see Section 4.7 for risk estimates based on occupational exposure scenarios) (continued)

Basis	Inhalation unit risk estimate[a] (per μg/m^3)[b]
Breast cancer mortality in females based on human data (NIOSH)—linear regression of categorical results	1.2×10^{-4}
Total cancer incidence based on human data (NIOSH)	6.2×10^{-4}

[a]Technically, the values listed in this table are not all unit risk estimates as defined by EPA, but they are all potency estimates that, when multiplied by an exposure value, give an estimate of extra cancer risk. These potency estimates are not intended for use with continuous lifetime exposure levels above 140 μg/m^3. See Section 4.7 for risk estimates based on occupational exposure scenarios. Preferred estimates are in bold.

[b]To convert unit risk estimates to (ppm)$^{-1}$, multiply the (μg/m^3)$^{-1}$ estimates by 1,830 (μg/m^3)/ppm.

[c] Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and because of the lack of chemical-specific data, EPA assumes increased early-life susceptibility and recommends the application of ADAFs, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b), for exposure scenarios that include early-life exposures. For the full lifetime (upper bound) unit risk estimate presented here, ADAFs have been applied, as described in Section 4.4.

[d]These (upper bound) unit risk estimates are intended for use in ADAF calculations and less-than-lifetime adult exposure scenarios (U.S. EPA, 2005b). Note that these are not the same as the unit risk estimates derived directly from the human data in Section 4.1 under the assumption that RRs are independent of age. Under that assumption, the key unit risk estimates were 4.8×10^{-4} per μg/m^3 for lymphoid cancer incidence, 9.5×10^{-4} per μg/m^3 for breast cancer incidence from the best-fitting 2-piece linear spline model, and 1.2×10^{-3} per μg/m^3 for the combined cancer incidence risk from those two cancers. See Section 4.4 for the derivation of the adult-based unit risk estimates.

[e]These are not upper-bound risk estimates but, rather, estimates based on linear extrapolation from the EC_{01}. ADAFs should be applied if early-life exposure occurs, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b).

Table 4-25. Comparison of unit risk estimates[a]

Assessments	Data source	Inhalation unit risk estimate[b] (per µg/m^3)
Based on human data		
EPA (this document)[c]	Lymphoid cancer incidence in sterilizer workers (NIOSH)[d]	7.2×10^{-4}
	Breast cancer incidence in female sterilizer workers (NIOSH)[e]	1.4×10^{-3}
	Total cancer risk based on the NIOSH data	1.8×10^{-3}
Kirman et al. (2004)	Leukemia mortality in combined NIOSH and UCC cohorts (earlier follow-ups)	4.5×10^{-8} Range of 1.4×10^{-8} to 1.4×10^{-7} [f]
Valdez-Flores et al. (2010)	multiple individual cancer endpoints, including all lymphohematopoietic, lymphoid, and breast cancers, in combined updated NIOSH and updated UCC cohorts	5.5×10^{-7} to 1.6×10^{-6} [g]
Based on rodent data		
EPA (this document)[c]	Female mouse tumors	7.6×10^{-5}
Kirman et al. (2004)	Mononuclear cell leukemia in rats and lymphomas in mice	2.6×10^{-8} to 1.5×10^{-5} [h]

[a]Upper-bound estimates except where footnoted to indicate that estimates are based on EC values (i.e., estimates with footnotes f and g).

[b]Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and in the absence of chemical-specific data, EPA assumes increased early-life susceptibility, in accordance with EPA's *Supplemental Guidance* (U.S. EPA, 2005b), and for the EPA lifetime unit risk estimates presented in this table, ADAFs have been applied, as described in Section 4.4. The corresponding adult-based unit risk estimates are 4.4×10^{-4} $(\mu g/m^3)^{-1}$ for human-based lymphoid cancer incidence, 8.2×10^{-4} $(\mu g/m^3)^{-1}$ for human-based breast cancer incidence, 1.1×10^{-3} $(\mu g/m^3)^{-1}$ for human-based total cancer incidence, and 4.6×10^{-5} $(\mu g/m^3)^{-1}$ for rodent-based total cancer incidence. 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, with the exception of the Valdez-Flores et al. (2010) estimates, which are purported to include the ADAFs, but the ADAFs were in fact misapplied and have essentially no impact (see Appendix A.2.20).

[c]See Table 4-24 in Section 4.5 for a more complete summary of estimates from this assessment. See Section 4.7 for risk estimates for occupational exposure scenarios.

[d]For lymphoid cancer mortality, the ADAF-adjusted lifetime unit risk estimate is 3.3×10^{-4} $(\mu g/m^3)^{-1}$ and the adult-based unit risk estimate is 2.0×10^{-4} $(\mu g/m^3)^{-1}$.

[e]For breast cancer mortality, the ADAF-adjusted lifetime unit risk estimate is 4.0×10^{-4} $(\mu g/m^3)^{-1}$ and the adult-based unit risk estimate is 2.4×10^{-4} $(\mu g/m^3)^{-1}$.

[f]Estimates based on linear extrapolation from EC0001−EC000001 obtained from the quadratic model.

[g]Estimates based on range of EC(1/million)s of 0.001−0.003 ppm obtained from the model RR = $e^{(\beta \times \text{exposure})}$ for relevant cancer endpoints.

[h]Estimates based on quadratic extrapolation model below the observable range of the data (i.e., below the LEC_{10} or LEC_{01} obtained using multistage model) with various points of departure (LEC_{01}–LEC_{000001}) for final linear extrapolation (see Section 4.4.2).

The Kirman et al. (2004) values are different from those in the current document because of the different assumptions inherent in the Kirman et al. (2004) approach and because the study used unpublished data from earlier follow-ups of the two cohorts. 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 extra risk level (1%) for establishing the POD, whereas Kirman et al. (2004) used a risk level of 10^{-5} for their best estimate and a risk range of 10^{-4} to 10^{-6} for their range of values. The extra risk level and the corresponding POD are not critical with the linear model; however, with the quadratic model used by Kirman et al. (2004), the lower the risk level (and hence the POD), the greater the impact of the quadratic model and the lower the resulting unit risk estimates.

In addition, EPA (1) uses data for lymphoid cancers (and female breast cancers) rather than leukemias, (2) includes ages up to 85 years in the life-table 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, (5) uses the results of lagged analyses rather than unlagged analyses, and (6) uses adult-based unit risk estimates in cojunction with ADAFs (see Section 4.4) to derive the lifetime unit risk estimates.

Another key difference is that Kirman et al. (2004) 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 cancers suggest a supralinear exposure-response relationship (see Section 4.1.1.2 and Figures 4-1 and 4-2), 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 Kirman et al. (2004) (see Section 3.4).

The Valdez-Flores et al. (2010) unit risk estimates (see Table 4−25) are similarly much lower than those in the current document because of the different assumptions used. A key difference is that EPA uses a linear model or a two-piece linear spline model in the range of observation rather than an exponential model ($RR = e^{\beta \times exposure}$), which was used by Valdez-Flores et al. (2010) despite its lack of fit. Then, EPA uses a higher extra risk level (1%) for establishing the POD for linear extrapolation, whereas Valdez-Flores et al. (2010) used a risk level of 10^{-6}. In addition, EPA (1) includes ages up to 85 years in the life-table analysis rather than stopping at 70 years, (2) calculates unit risk estimates for cancer incidence as well as mortality, (3) uses a lower bound as the POD rather than the maximum likelihood estimate, and (4) uses the results of lagged analyses rather than unlagged analyses. See Appendix A.2.20 for a

more detailed discussion of the differences between the EPA and Valdez-Flores et al. (2010) analyses.

4.6.2. Unit Risk Estimates Based on Laboratory Animal Studies

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. (2004) obtained a unit risk range of 3.9×10^{-6} $(\mu g/m^3)^{-1}$ to 1.5×10^{-5} $(\mu g/m^3)^{-1}$. Alternatively, Kirman et al. (2004) 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} $(\mu g/m^3)^{-1}$ to 4.9×10^{-6} $(\mu g/m^3)^{-1}$. These values are all smaller than the unit risks derived from the rodent data in this document.

4.7. RISK ESTIMATES FOR SOME OCCUPATIONAL EXPOSURE SCENARIOS

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 $\mu g/m^3$ (email dated October 3, 2005, from Mark Morris, EPA, to Jennifer Jinot, EPA), i.e., roughly 0.5−1 ppb, and are not applicable to higher exposures, including some occupational exposure levels. However, occupational exposure levels of EtO are of concern to EPA when EtO is used as a pesticide (e.g., sterilizing agent or fumigant). The occupational exposure scenarios of interest to EPA include some cumulative exposures corresponding to exposure levels in the nonlinear range of some of the models (i.e., above the maximum exposure level at which the low-dose-linear unit risk estimates apply). Therefore, extra risk estimates were calculated for a number of occupational exposure scenarios of possible concern. Extra risk estimates are estimates of the extra cancer risk above background and are the same type of estimate that one gets from multiplying a unit risk estimate by an exposure level. In this case, the exposure level is used directly in the exposure-response model, thus accounting for any nonlinearities in the model above the range of exposure levels for which the linear unit risk estimate is applicable. For these occupational exposure scenarios, exposure-response models based on data 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). (Note that the current Occupational Safety and Health Administration Permissible Exposure Limit is 1 ppm [8-hour TWA].)

For *lymphoid cancer* mortality in both sexes, the best-fitting (natural) log cumulative exposure Cox regression model (see Steenland reanalyses in Appendix D; see also Section 4.1.1.2), lagged 15 years, was used. The log cumulative exposure Cox regression model was the best-fitting model for lymphoid cancer in males in the Steenland et al. (2004) study, and the same model form is used here but with the data from both sexes. Although this model was deemed too steep in the low-exposure region to be useful for the derivation of unit risk estimates for lower (environmental) exposures, the model is well suited for the occupational exposure scenarios of interest in this assessment because the corresponding cumulative exposures are well within the range of the cumulative exposures in the NIOSH cohort. The model was statistically significant ($p = 0.02$) and provided a better fit, based on AIC, than the two-piece spline models that were considered as alternative models in Section 4.1.1.2 (the AICs were 460.426, 461.847, and 461.48 for the log cumulative exposure Cox regression, log-linear two-piece spline and linear two-piece spline models, respectively [as reported in Section D.3 of Appendix D]; a lower AIC indicates a better fit), as well as a more plausible, smoothly curved exposure-response relationship than the two-piece spline models, both of which, with knots at 100 ppm × days, had a very steep rise and then a very sharp change in slope at the knot. In addition, the log cumulative exposure Cox regression model had a slightly lower AIC (460.426 versus 460.54) than the log cumulative exposure linear model (see Section D.3.c of Appendix D) and has the advantage of being a standard epidemiological model for continuous exposure data (the Cox regression model, albeit with log cumulative exposure to accommodate the supralinearity of the exposure-response data). The log cumulative exposure linear model yields slightly higher RR estimates than the log cumulative exposure Cox regression model, as can be seen by comparing the log cumulative exposure models in Figures D-3b and D-3c in Appendix D, and would thus result in slightly higher extra risk estimates than the log cumulative exposure Cox regression model. For example, the MLEs of extra risk from the log cumulative exposure linear model would range from about 23% higher for the 0.1 ppm 8-hour TWA to 6% higher for the 1 ppm 8-hour TWA.

The extra risk results for lymphoid cancer mortality and incidence in both sexes for the log cumulative exposure Cox regression model are presented in Table 4-26. For lymphoid cancer incidence, the exposure-response relationship was assumed to be the same as for mortality (see Section 4.1.1.3). As can be seen in Table 4-26, 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 4-1) but rather in the steep low-exposure region, which is 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 lower exposures (see Section 4.1.1.2; Appendix D). Furthermore, if one is using the linear regression model in this range and also estimating risks for exposure levels in the range between about 0.08 and 0.6 ppm (near where the linear regression and log cumulative exposure Cox regression models meet) 8-hour TWA, then one might want to use the linear regression model for the entire range up to 0.6 ppm 8-hour TWA to avoid a discontinuity between the two models; thus, results for the linear regression model for exposure levels up to 0.6 ppm 8-hour TWA are also presented in Table 4-26. While the best-fitting continuous exposure model, the log cumulative exposure Cox regression model, would generally be preferred in the exposure range between 0.08 and 0.6 ppm 8-hour TWA, there is model uncertainty, so the use of either model could be justified. For exposures higher than where the linear regression and log cumulative exposure Cox regression models meet, the log cumulative exposure model exclusively is recommended. The models used to derive the extra risk estimates presented in Table 4-26 for lymphoid cancer for the occupational exposure scenarios are displayed in Figure 4-7 over the range of occupational cumulative exposures of interest; the categorical results are included for comparison.

For *breast cancer*, incidence data were available from the NIOSH incidence study; thus, only incidence estimates were calculated. In addition to being the preferred type of cancer risk estimate, the breast cancer incidence risk estimates are based on more cases than were available in the mortality study 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 have incomplete ascertainment of breast cancer cases.

For breast cancer incidence in the subcohort with interviews, a number of Cox regression exposure-response models from the Steenland et al. (2003) breast cancer incidence study fit almost equally well (see Section 4.1.2.3). 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. The latter model was omitted from the calculations because the inclusion of a 15-year lag for the development of breast cancer was considered more biologically realistic than not including a lag. Steenland et al. (2003) also provide a duration-of-exposure Cox regression model with a marginally better fit; however, models using duration of exposure are less useful

Table 4-26. Extra risk estimates for lymphoid cancer in both sexes for various occupational exposure levels[a]

8-hr TWA (ppm)	Lymphoid cancer mortality				Lymphoid cancer incidence[b]			
	Log cumulative exposure Cox regression model[c]		Linear regression model[d]		Log cumulative exposure Cox regression model[c]		Linear regression model[d]	
	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL
0.1	0.014	0.032	0.003	0.007	**0.031**	**0.071**	**0.007**	**0.016**
0.2	0.016	0.038	0.007	0.014	**0.035**	**0.084**	**0.014**	**0.031**
0.3	0.017	0.042	0.010	0.022	**0.038**	**0.093**	**0.021**	**0.047**
0.4	0.018	0.045	0.013	0.029	**0.040**	**0.099**	**0.028**	**0.062**
0.5	0.018	0.047	0.016	0.036	**0.042**	**0.10**	**0.035**	**0.076**
0.6	0.019	0.049	0.019	0.042	**0.043**	**0.11**	**0.042**	**0.090**
0.7	0.019	0.051	--	0.049	**0.044**	**0.11**	--	--
0.8	0.020	0.052	--	--	**0.045**	**0.12**	--	--
0.9	0.020	0.054	--	--	**0.046**	**0.12**	--	--
1.0	0.021	0.055	--	--	**0.047**	**0.12**	--	--

[a]Assuming a 35-yr exposure between ages 20 and 55 years (see Section 4.7).
[b]Assumes same exposure-response relationship as for lymphoid cancer mortality.
[c]From the best-fitting log cumulative exposure Cox regression model for lymphoid cancer mortality in both sexes; 15-yr lag (see Appendix D; see also Section 4.1.1.2).
[d]Linear regression of categorical results for both sexes (see Appendix D; 15-yr lag), excluding the highest exposure group (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 Cox regression model.

MLE: maximum likelihood estimate; UCL: (one-sided) upper confidence limit estimate.

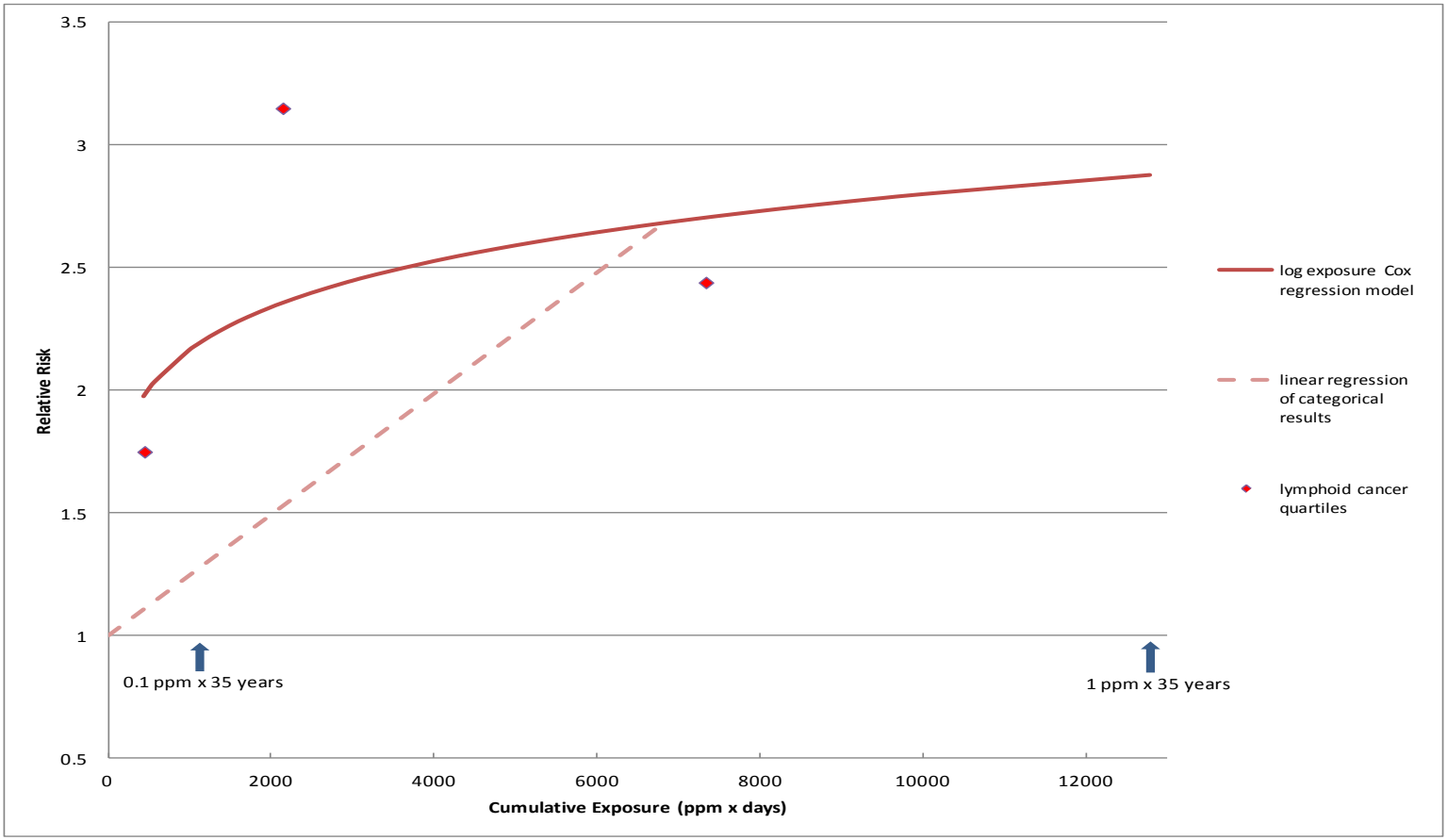

Figure 4-7. RR estimates for lymphoid cancer from occupational EtO exposures (with 15-year lag).

Lymphoid cancer models (see Section 4.1.1.2): log cumulative exposure Cox regression model; categorical results from Cox regression model; linear regression of categorical results, excluding highest exposure group.

for estimating exposure-related risks, and duration of exposure and cumulative exposure are correlated. Thus, only the lagged cumulative exposure models are considered here.

The extra risk estimates for breast cancer incidence in females from the lagged cumulative exposure and log cumulative exposure Cox regression models listed above are presented in Table 4-27. As can be seen in Table 4-27, the extra risk estimates for the lagged log cumulative exposure and cumulative exposure models differ substantially. Furthermore, the categorical Cox regression 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 4-5). (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, the maximum of which is 12,775 ppm × days.) Therefore, the two-piece linear spline model (with a 15-year lag) (see Section 4.1.2.3) was also used to calculate the extra risk estimates. The two-piece linear spline model provides a better fit to the data than the log cumulative exposure or cumulative exposure Cox regression models, as indicated by a lower AIC value (1,950.9 for two-piece linear spline model vs. 1,956.2 for the log cumulative exposure Cox regression model and 1,956.8 for the cumulative exposure Cox regression model; Table 4-12 and Appendix D). In fact, the two-piece linear spline model provided the best fit to the breast cancer incidence data of all the models investigated in Section 4.1.2.3, and it provides the best representation of the categorical RR results, particularly for the range of cumulative exposures for the occupational exposure scenarios of interest (see Figures 4-5, 4-6, and 4-8). The extra risk estimates calculated using the two-piece linear spline model are also presented in Table 4-27 and are the preferred estimates because they are derived from the best-fitting model.

In addition, extra risk estimates for breast cancer incidence in females from the continuous linear model (with a 15-year lag) (see Section 4.1.2.3) are presented in Table 4-27. This model, with an AIC of 1,952.3 (see Table 4-12), was the second-best-fitting model and also provided a good visual fit to the categorical data (see Figure 4-6). Moreover, the two best-fitting models (i.e., the continuous linear model and the two-piece linear spline model) span the range of RR estimates from the three best–fitting models investigated in Section 4.1.2.3 (the third being the two-piece log-linear spline model) over the range of cumulative exposures for the occupational exposure scenarios of interest in this assessment (see Figure 4-6). Comparing the results of the two best-fitting models shows that the extra risk estimates differ by just under

Table 4-27. Extra risk estimates for breast cancer incidence in females for various occupational exposure levels[a,b]

8-hr TWA (ppm)	Log cumulative exposure Cox regression model[c]		Cumulative exposure Cox regression model[c]		Continuous linear model[d]		Two-piece linear spline model[e]	
	MLE	95% UCL	MLE	95% UCL	MLE	95% UCL[f]	MLE	95% UCL[g]
0.1	0.055	0.11	0.0013	0.0023	0.0042	0.0081	**0.016**	**0.031**
0.2	0.061	0.12	0.0026	0.0046	0.0084	0.016	**0.032**	**0.061**
0.3	0.065	0.13	0.0040	0.0069	0.012	0.024	**0.048**	**0.090**
0.4	0.068	0.14	0.0053	0.0092	0.017	0.032	**0.063**	**0.118**
0.5	0.070	0.14	0.0067	0.012	0.021	0.040	**0.075**	**0.139**
0.6	0.072	0.14	0.0081	0.014	0.025	0.048	**0.081**	**0.150**
0.7	0.073	0.15	0.0095	0.017	0.029	0.055	**0.086**	**0.157**
0.8	0.074	0.15	0.011	0.019	0.033	0.063	**0.089**	**0.162**
0.9	0.076	0.15	0.012	0.022	0.037	0.070	**0.093**	**0.167**
1.0	0.077	0.16	0.014	0.024	0.041	0.078	**0.095**	**0.171**

[a]Assuming a 35-yr exposure between ages 20 and 55 years.
[b]From incidence data for subcohort with interviews; invasive and in situ tumors (Steenland et al., 2003).
[c]Cox regression models from Steenland et al. (2003, Table 5), with 15-yr lag.
[d]Linear model with cumulative exposure as a continuous variable (see Section 4.1.2.3 and Section D.2 of Appendix D).
[e]Two-piece linear spline model results for occupational exposures use both spline segments (see Section D.2 of Appendix D), knot at 5,800 ppm × days; with 15-yr lag. For the 95% UCL, for exposures below the knot, RR = 1 + (β1 + 1.645 × SE1) × exposure; for exposures above the knot, RR = 1 + (β1 × exp + β2 × (exp-knot) + 1.645 × sqrt(exp^2 × var1 + $(exp\text{-}knot)^2$ × var2 + 2 × exp × (exp-knot) × covar)), where exp = cumulative exposure, var = variance, covar = covariance (see Section D.2 of Appendix D for the parameter values).
[f]Confidence intervals used in deriving the 95% UCLs were estimated employing the Wald approach. Confidence intervals for linear RR models, however, in contrast to those for the log-linear RR models, may not be symmetrical. EPA also evaluated application of a profile likelihood approach for the linear RR models (Langholz and Richardson, 2010), which allows for asymmetric CIs, for comparison with the Wald approach. Using the profile likelihood method, the resulting extra risk estimates for breast cancer incidence for the continuous linear model would have been about 29% higher than those obtained using the Wald approach.

Table 4-27. Extra risk estimates for breast cancer incidence in females for various occupational exposure levels[a,b] (continued)

[g]Confidence intervals used in deriving the 95% UCLs were estimated employing the Wald approach. Confidence intervals for linear RR models, however, in contrast to those for the log-linear RR models, may not be symmetrical. EPA also evaluated application of a profile likelihood approach for the linear RR models (Langholz and Richardson, 2010), which allows for asymmetric CIs, for comparison with the Wald approach. Using the profile likelihood method, the resulting extra risk estimates for breast cancer incidence for the low-exposure linear spline segment (i.e., below 0.4 ppm 8-hr TWA) would have been about 34% higher than those obtained using the Wald approach. Calculating the profile likelihood CIs in the region of the second spline segment is computationally difficult and was not pursued here.

MLE: maximum likelihood estimates; UCL: (one-sided) upper confidence limit estimate.

fourfold at the lowest exposure level (0.1 ppm 8-hour TWA) and the difference tapers to just over twofold at the highest exposure level (1 ppm 8-hour TWA), with the estimates of the best-fitting model, the two-piece linear spline model, yielding the higher extra risk estimates across the range.

Finally, for comparison, maximum likelihood estimates (MLEs) of extra risk for the log cumulative exposure Cox regression model with a 10-year lag were calculated. The model with a 10-year lag also provided a statistically significant fit to the data ($p = 0.03$), whereas, the models with 5- and 15-year lags did not. These estimates ranged from 0.067 for 0.1 ppm exposure to 0.094 for 1.0 ppm exposure. Thus, the MLEs of extra risk with a 10-year lag were about 20% higher than those with the 15-year lag.

The continuous models (with a 15-year lag) considered for deriving the extra risk estimates for breast cancer incidence in females for the occupational exposure scenarios are displayed in Figure 4-8 over the range of occupational cumulative exposures of interest. Categorical results are also presented for comparison (deciles from the categorical linear model are presented because it had a better fit than the log-linear categorical model, as indicated by the AICs, which were 1,963.9 and 1,966.9, respectively; Appendix D). The recommended model is the two-piece linear spline model; this was the best-fitting continuous model of those evaluated in this assessment, and it provides the best visual fit in comparison to the categorical results in the range of the occupational exposure scenarios of interest. As shown in Figure 4-8, the log cumulative exposure Cox regression model is too flat across the range of exposures of interest, apparently overestimating the risks at lower exposures and underestimating those at higher exposures. It also appears from Figure 4-8 that the cumulative exposure Cox regression model and the linear model both underestimate risks across the range of exposures of interest. This is consistent with the analysis presented in Section D.1 of Appendix D showing the strong influence of the upper tail of cumulative exposures on the results of the cumulative exposure Cox regression model. The responses in the upper tail of exposures are relatively dampened, such that when the highest 5% of exposures (exposures > 27,500 ppm × days, which are well in excess of the exposures of corresponding to the occupational exposure scenarios considered here) are excluded, the slope of the Cox regression model is substantially increased (e.g., at 10,000 ppm × days, the RR estimate increases from about 1.1 to almost 1.5; see Figure D-1d in Appendix D). This strong influence of the upper tail of exposures would similarly attenuate the slope of the (continuous) linear model, resulting in underestimation of the lower-exposure risks. The two-piece linear spline model, on the other hand, is more flexible, and the influence of the upper tail of exposures would be primarily on the upper spline segment; thus, the two-piece model is able to provide a better fit to the lower-exposure data.

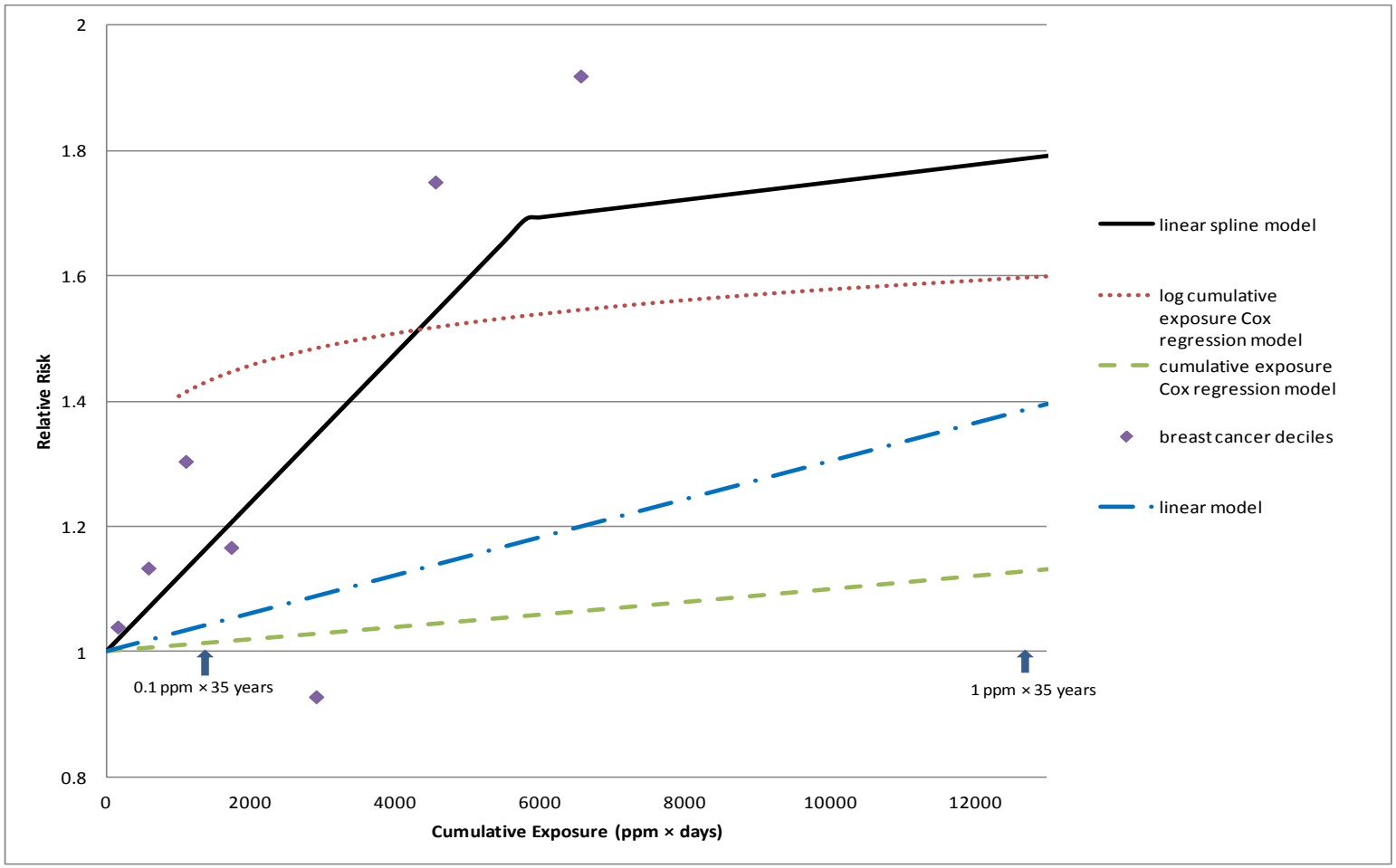

Figure 4-8. RR estimates for breast cancer incidence from occupational EtO exposures (with 15-year lag).

Breast cancer models (see Section 4.1.2.3): linear 2-piece spline model, with knot at 5,800 ppm × days; log cumulative exposure Cox regression model; (cumulative exposure) Cox regression model; continuous linear model; categorical results (deciles) from continuous linear model.

For the *total cancer risk* combined across the two cancer types, the MLE can be obtained directly by summing the MLEs for the individual cancer types. An upper bound can be approximated by summing the 95% UCL estimates for the individual cancer types; however, this will overestimate the corresponding 95% UCL on total cancer risk.

Although there is model *uncertainty*, as discussed above, there is less overall uncertainty associated with the extra risk estimates for occupational exposure scenarios than with the unit risk estimates for environmental exposures. The extra risk estimates are derived for occupational exposure scenarios that yield cumulative exposures well within the range of the exposures in the NIOSH study. Moreover, the NIOSH study is a study of sterilizer workers who used EtO for the sterilization of medical supplies or spices (Steenland et al., 1991); thus, the results are directly applicable to workers in these occupations, and these are among the occupations of primary concern for current occupational EtO exposures.

Calculation of Extra Risk Estimates for Other Occupational Exposure Scenarios:

Some detailed guidance is provided here for calculating extra risk estimates outside of the range of occupational scenarios considered above. Note that for 35-year exposures to exposure levels between the exposure levels presented in Tables 4-26 and 4-27, e.g., 0.15 ppm, one could interpolate between the extra risk estimates presented for the closest exposure levels on either side.

<u>For occupational exposures with *durations other than 35 years*:</u>

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 lymphoid cancer in both sexes 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 risks by calculating the cumulative exposure and finding the extra risks for a similar cumulative exposure in Tables 4-26 and 4-27. For a more precise estimation, or for exposure scenarios of much shorter duration or for specific age groups, one should do the calculations using a life-table analysis, as presented in Appendix E but modified for the specific exposure scenarios.

For occupational exposures *below 0.1 ppm*:

For lymphoid cancer, use of the log cumulative exposure Cox regression model is not advised below 0.1 ppm (× 35 years). Instead, the low-exposure continuation of the linear regression model presented in Table 4-26 of the assessment is recommended. For 35-year exposures, the following formulae would apply:

95% UCL on extra risk for lymphoid cancer incidence ≈ (8-h TWA occ exp [in ppm]) × (0.016/0.1 ppm) = (8-h TWA occ exp [in ppm]) × (0.16/ppm)

MLE of extra risk for lymphoid cancer incidence = (8-h TWA occ exp [in ppm]) × (0.007/0.1 ppm) = (8-h TWA occ exp [in ppm]) × (0. 07/ppm)

If one is considering occupational exposure scenarios using a range of 8-h TWA exposure levels on both sides of 0.1 ppm, one might want to use the linear regression model for all the exposure levels up to about 0.6 ppm 8-h TWA (approximately where the linear regression model intersects the log cumulative exposure Cox regression model) to avoid the discontinuity between the two models below where they intersect. Note that the extra risk estimates from the different models differ by at most about 4.5-fold (at 0.1 ppm) and that there is model uncertainty in this range, so the use of either model could be justified. Above where the models intersect, only the log cumulative exposure Cox regression model should be used.

For breast cancer, the low-exposure continuation of the two-piece linear spline model presented in Table 4-27 of the assessment is recommended. For 35-year exposures, the following formulae would apply:

95% UCL on extra risk for breast cancer incidence ≈ (8-h TWA occ exp [in ppm]) × (0.031/0.1 ppm) = (8-h TWA occ exp [in ppm]) × (0. 31/ppm)

MLE of extra risk for breast cancer incidence = (8-h TWA occ exp [in ppm]) × (0.016/0.1ppm) = (8-h TWA occ exp [in ppm]) × (0. 16/ppm)

Above 0.1 ppm 8-h TWA, use the two-piece linear spline model results in Table 4-27 of the assessment.

Alternatively, for exposures below 0.1 ppm, one could use the formulae presented below, which are based on the unit risk estimates presented in Tables 4-22 (for 95% UCLs) and Table 4−23 (for MLEs), with conversions for adjusting occupational to environmental exposures. Note, however, that the extra risk results for 35 years of exposure based on these unit risk values do not exactly match the values in Tables 4-26 and 4-27 for the linear models (the formulae below yield extra risk estimates that are 15−20% lower than the values in Tables 4-26 and 4-27 for the low end of the exposure range [e.g., 0.1–0.4 ppm] where the comparison with the unit-risk-based estimates is appropriate). This is because the results in Tables 4-26 and 4-27 are based on life-table analyses, which take into account age-specific background rates of the cancers and ages of exposure (assumed to be from 20 to 55 years of age in these occupational exposure scenarios), whereas the formulae below are approximations that do not take age-specific considerations into account. The advantage of the formulae based on the unit risk values is that they can incorporate durations other than ~ 35 years.

8-h TWA occ exp [in ppm] × (10 m^3/day/20 m^3/day) × (240 days/year/365 days/year) × (35 years/70 years) = (continuous lifetime) env exp [in ppm]
(Note that for exposure durations other than 35 years, replace 35 years with the alternate duration in the formula above.)

———————

95% UCL on extra risk for lymphoid cancer incidence ≈ 0.795/ppm × env exp [in ppm]

MLE of extra risk for lymphoid cancer incidence = 0.356/ppm × env exp [in ppm]

———————

95% UCL on extra risk for breast cancer incidence (in females) = 1.50/ppm × env exp [in ppm]

MLE of extra risk for breast cancer incidence (in females) = 0.776/ppm × env exp [in ppm]

REFERENCES

This reference list includes all the references cited in the document except for Appendix B, which is a reference list pertaining to Figure 3−3, and Appendix J, which includes some more recent references. References added after the 2007 external peer review are also listed separately in Appendix I. References identified in a May 2013 literature search but appearing after the 30 June 2010 cutoff date for literature inclusion into this carcinogenicity assessment are cited and discussed in Appendix J.

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