

BEFORE THE
SCIENCE ADVISORY BOARD - ETHYLENE OXIDE CARCINOGENICITY

COMMENTS OF THE ETHYLENE OXIDE/ETHYLENE GLYCOLS PANEL
ON EPA'S DRAFT EVALUATION OF CARCINOGENICITY OF ETHYLENE OXIDE
ADDRESSING THE SAB'S CHARGE QUESTIONS

Notice of Public Meeting of the Ethylene Oxide Review)
Panel to Review the EPA's Draft Assessment: Evaluation)
of the Carcinogenicity of Ethylene Oxide)
71 Fed. Reg. 66328 (Nov. 14, 2006))

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January 8, 2007

EXECUTIVE SUMMARY

The Ethylene Oxide/Ethylene Glycols Panel (Panel) of the American Chemistry Council submits these additional comments to the Science Advisory Board (SAB) Ethylene Oxide Carcinogenicity Review Panel in response to the *Federal Register* notice soliciting public comment on the U.S Environmental Protection Agency's (EPA) draft *Evaluation of the Carcinogenicity of Ethylene Oxide* (Draft Cancer Assessment). The SAB will be considering public comment during its January 18-19, 2007, meeting. The Panel is pleased to provide these additional comments, addressing the Charge Questions to the SAB and the Panel's additional Charge Questions submitted to the SAB on December 1, 2006. These were also discussed during the SAB's December 8, 2006, teleconference.

Panel members manufacture most of the ethylene oxide (EO) produced in the United States or use large amounts of EO. As manufacturers and users of EO, the validity of the scientific basis for the Draft Cancer Assessment and its suitability for purposes of serving as the basis for regulatory determinations are highly important to the Panel.

As more fully discussed in these comments, the Panel believes the Draft Cancer Assessment fails to provide a scientifically justified basis to assess potential health risk issues from exposure to EO. The many deficiencies in the Draft Cancer Assessment greatly overstate the potential risk to human health that low levels of EO inhalation exposure may pose. Key among these deficiencies include:

- **The Draft Cancer Assessment Does Not Use the Best Available Science as Required under the Information Quality Act and Cancer Guidelines.**
 - EPA based its evaluation on summaries of statistics available in various publications. These data, however, are not sufficient to conduct valid dose-response modeling. EPA should have based its calculations on readily available National Institute of Occupational Safety and Health (NIOSH) data for individual subjects from the cohort mortality study.
 - EPA did not use all available epidemiologic data, including the Union Carbide Corporation (UCC) data and all NIOSH data that were available at the time EPA conducted its assessment. In particular, the Greenberg, *et al.* (1990) UCC study reported the consistency of the death certificate diagnosis with a pathology review of medical records for leukemia cases, a validation not conducted for cases in the NIOSH study.

- EPA Should Not Have Relied Entirely on Males in Its Assessment of Lymphohematopoietic (LH) Cancer Mortality. To be scientifically defensible, EPA's LH cancer risk characterization must include both males and females, consistent with a "weight-of-evidence" approach that relies on *all* relevant information. In the NIOSH retrospective study, increased risks of LH cancer were observed in males but not females, even though the NIOSH cohort was large and diverse, and consisted of more women than men. EPA's exclusive reliance on male data is scientifically unsound because it lacks a mechanistic justification for treating males and females differently with respect to LH.
- **EPA Should Recognize That EO Is Both a Weak Mutagen and Weak Animal Carcinogen.** If genotoxicity is considered the means by which a chemical induces cancer, it follows that it will not induce a cancer under conditions where it does not induce mutations, at either the chromosome or gene level, thus providing a mechanistic basis for estimating carcinogenicity. A chemical's carcinogenic potency is necessarily related to its mutagenic potency. EO is a DNA-reactive genotoxic agent, as demonstrated by numerous *in vitro* and *in vivo* studies. It is only weakly mutagenic. It is therefore not surprising that no exposure-related tumors were observed in rats exposed to EO, even at the 100 parts per million concentration level, at the 18 month sacrifice, and the most sensitive tumor type (*i.e.*, splenic mononuclear cell leukemia) did not significantly increase in the exposed rats until 23 months- almost the end of their lifetime of exposures (Snellings *et al.*, 1984). EPA's analysis should have reconciled these findings with its estimation of EO's carcinogenic potency, but the analyses do not do so.
 - Among 26 alkylating agents studies by Vogel, *et al.* (1998), EO showed the second lowest carcinogenic potency.
 - Previous assessments of EO inhalation time to tumor in rats showed that the increased risks observed at higher experimental doses did not extend to the lowest experimental dose. To comply with the Cancer Guidelines, EPA should include these and other relevant animal data in a weight-of-evidence characterization of EO.
- **EPA's Risk Estimates Do Not Pass Simple Reality Checks.**
 - The results of the Draft Cancer Assessment (resulting in negligible risk only at levels less than a part per trillion (ppt)), are not scientifically defensible when compared with

the results generated for other substances that are considered potent mutagens and/or potent carcinogens, and do not comport with the results of assessments EPA has undertaken.

- The results of the Draft Cancer Assessment are at odds with EPA's conclusion that EO is a potent (*de minimis* level < 1 ppt) human carcinogen and EO's potency seen in animal studies.
- EPA's draft unit risk values for EO are not applicable to the general public. The Draft Cancer Assessment grossly over predicts the observed number of LH cancer mortalities in the study upon which it is based by more than 60-fold. Further, EPA's *de minimis* value is about 50 times lower than the lowest ambient concentration found at remote coastal locations. Based upon PBPK simulations, endogenous concentrations of EO in humans are approximately 400-1700 times greater than EPA's proposed *de minimis* value of 0.00036 part per billion.
- EPA's draft unit risk values for EO are unreasonably large, given the non-conclusive evidence of carcinogenicity in a large body of epidemiology studies, the weak mutagenicity data, and the lack of cancer response in rodents until very late in their exposure lifetime. EPA must make the best use of all of the epidemiology, toxicology, and genotoxicity data for EO that provide valid information on the relationship between exposure and cancer response to improve the reasonableness of the unit risk values for EO.

- **Certain Policy Decisions EPA Implements in the Draft Cancer Assessment Are Scientifically Unsupported, Unprecedented, Overly Conservative, and Inappropriate.** EPA made several policy decisions that compounded greatly the inherent conservatism in the risk estimates. These include, among others: (1) EPA's reliance on the lower bound of the point of departure, rather than the best estimate when using human data, resulting in a 2- to 3-fold overestimate of risk; (2) use of background incidence rates with mortality-based relative rates, which rely on an unsupported assumption and which yields bias results; (3) EPA's assumption of an 85-year lifetime of continuous exposure and cumulative risk, rather than the more traditional 70-year lifetime, resulting in an increase in the lifetime excess risk estimate of approximately 3-fold; and (4) the application of adjustment factors for early-life exposures.

Consequently, the Panel believes that EPA's proposed unit risk value cannot be used reliably to estimate the potential risk to the general public from low levels of EO inhalation exposure with any reasonable degree of confidence. As discussed in more detail below, and in the Panel's December 8, 2006, comments to EPA, EPA should substantially revise the Draft Cancer Assessment to address these numerous scientific deficiencies and flaws.

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INTRODUCTION

The Ethylene Oxide/Ethylene Glycols Panel (Panel) of the American Chemistry Council submits these additional comments to the Science Advisory Board (SAB) Ethylene Oxide Carcinogenicity Review Panel in response to the *Federal Register* notice¹ soliciting public comment on the U.S. Environmental Protection Agency's (EPA) draft *Evaluation of the Carcinogenicity of Ethylene Oxide* (Draft Cancer Assessment).² The SAB will be considering public comment during its January 2007 meeting.³

These comments represent a distillation of the more extensive comments the Panel provided to EPA on December 8, 2006. These comments focus on the major scientific deficiencies of the Draft Cancer Assessment, including its:

- Failure to use the best available data and science;
- Exclusive and inappropriate reliance on epidemiological data on males only from a single study;
- Failure to identify ethylene oxide (EO) as a weak mutagen and animal carcinogen;
- Failure to pass simple reality checks; and
- Inclusion of scientifically unsupported new policy decisions that have not been appropriately reviewed.

By focusing on these major issues, the Panel's comments also address the additional Charge Questions the Panel offered during the SAB's December 8, 2006, teleconference, as well as many of the Charge Questions EPA posed to the SAB. For the SAB's convenience, specific Charge Questions are referenced throughout these comments. In addition, Appendix A includes a table that depicts which sections of the Panel's more extensive December 8, 2006, comments to EPA, correspond to the SAB Charge Questions, as well as those the Panel offered. The Panel adopts and incorporates by reference here its December 8, 2006, comments.

The members of the Panel manufacture most of the EO produced in the United States or use large amounts of EO.⁴ As manufacturers and users of EO, the validity of the scientific basis for the Draft Cancer Assessment and its suitability for purposes of serving as the

¹ 71 Fed. Reg. 66328 (Nov. 14, 2006).

² EPA External Review Draft, "Evaluation of the Carcinogenicity of Ethylene Oxide," EPA/635/R-06/003 (Aug. 2006).

³ 71 Fed. Reg. at 66329.

⁴ The EO members of the Panel are: ARC; BASF Corporation; Bayer Corporation; Celanese Chemicals, on behalf of itself and Old World Industries; The Dow Chemical Company; Eastman Chemical Company; Honeywell; Huntsman Chemical; Lyondell Chemicals LP, Sasol North America, Inc.; Shell Chemical LP; and Sunoco, Inc. The Panel is the successor organization to the American Chemistry Council's Ethylene Oxide Industry Council (EOIC).

basis for regulatory determinations are highly important to the Panel. EO is an important building block for a multitude of familiar products with hundreds of uses and is also a necessary public health tool that sterilizes critical medical devices. Without EO, over 50 percent of all medical products provided in pre-sterilized packaged form would become unavailable, including syringes, IV tubing, surgical trays, catheters, orthopedic implants, vascular stents, and many other devices.

I. THE DRAFT CANCER ASSESSMENT DOES NOT USE THE BEST AVAILABLE DATA AND SCIENCE AND THUS VIOLATES THE IQA AND CANCER GUIDELINES

Cancer risk assessments, including the Draft Cancer Assessment, are presumed to be “influential information” as set forth under the Information Quality Act (IQA). Thus, EPA’s Draft Cancer Assessment is subject to a rigorous standard of quality. In particular, the *substance* of the information must be “accurate, reliable, and unbiased.” EPA must use the *best available science* as well as “a ‘weight-of-evidence’ approach that considers all relevant information and its quality.”⁵ Similarly, EPA’s Guidelines for Carcinogen Risk Assessment emphasize “a critical analysis of all the available information that is relevant to assessing the carcinogenic risk,” rather than rely on default options⁶ -- as the starting point, EPA has incorrectly done this in the Draft Cancer Assessment.

I.A. EPA Uses Only Summary Measures in Steenland, *et al.* (2003, 2004) But Should Use the Individual Subject Data and Does Not Use All the Available NIOSH Data

This section addresses, in part, the SAB Charge Questions 1a, b, c, d; 2a, b; and 3.

The Centers for Disease Control and Prevention (CDC) provided the Panel with the National Institute of Occupational Safety and Health (NIOSH) cohort mortality data. EPA uses only the odds ratios (OR) for deaths due to all hematopoietic cancer⁷ (ICD-9, 200-208) and breast cancer mortality and incidence from the results of nested case-control analyses in the Steenland, *et al.* publications (2003, 2004). EPA was therefore restricted in its analyses to the summary statistics available in the publications. These data are not sufficient to conduct valid dose-response modeling. EPA needed to have based its calculations on the readily available NIOSH data for individual subjects from the cohort mortality study, not just the ORs from the publications of Steenland, *et al.* (2003, 2004). Analyses of data from the individual subjects give

⁵ EPA, Office of Environmental Information, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (Information Quality Guidelines) (Oct. 2002) at 21. “In this approach, a well-developed, peer-reviewed study would generally be accorded greater weight than information from a less well-developed study that had not been peer-reviewed, but both studies would be considered.” *Id.* at 26.

⁶ EPA, Risk Assessment Forum, Guidelines for Carcinogen Risk Assessment (Cancer Guidelines), EPA/630/P-03/001F (Mar. 2005) at 1-7.

⁷ EPA and these comments refer to “all hematopoietic cancer” as lymphohematopoietic (LH) cancer.

different results (at least 30-fold) than invalid analyses based on ORs from the publication.⁸

I.A.1. EPA Relies Primarily on the NIOSH Retrospective Study,
Failing to Consider Adequately All Relevant
Epidemiological Evidence

In the Draft Cancer Assessment, EPA reviews the individual epidemiology studies for evidence of carcinogenicity and concludes that these studies have a general pattern of excesses in the broad LH cancer category and constitute “strong” evidence of carcinogenicity. LH cancers include leukemia, non-Hodgkin’s lymphoma (NHL), Hodgkin’s disease, and multiple myeloma, however, and this assessment does not delve any deeper into the types of LH cancers reported in each study, before coming to this conclusion and selecting the response of LH cancers for its dose-response assessment, based on the results of the NIOSH mortality study (Steenland *et al.*, 2004). For example, myeloid leukemias predominated in the Union Carbide Corporation (UCC) study (Greenberg *et al.*, 1990; Teta *et al.*, 1993), while NIOSH’s results support an excess of lymphoid tumors, including lymphocytic leukemia. Two of the studies with the longest follow-up of manufacturing and hospital sterilant workers reported no cases of multiple myeloma (Teta *et al.*, 1993; Coggon *et al.*, 2004). None of the studies reported excess of multiple myeloma. In the update of the Shore, *et al.* meta-analysis (Teta *et al.*, 1999), there was a suggestion of an increase for leukemia in the longest duration exposed and the longest follow-up groups of workers, but not so for NHL. This review included data from the prior NIOSH mortality study (Steenland *et al.*, 1991). A total of 53 leukemia deaths were reported in the epidemiology studies published through 2004 (including Divine (1990), not reviewed by EPA) and 50 were expected for an overall standardized mortality ratio (SMR) of 1.06 (95%CI: 0.79-1.39). For NHL, there were 59 observed and 53 expected (SMR=1.11; 95%CI: 0.85-1.44) deaths in studies through 1999. The Steenland, *et al.* (2004) results related to LH and lymphoid cancers are dependent on the type of statistical analysis conducted, including the exposure metric and gender. The results of the extensive body of human data certainly do not support a conclusion of strong evidence of carcinogenicity. Furthermore, selection of an appropriate response should not rely on a single study but consider consistency with the entire body of human evidence at the greatest level of specificity possible.

EPA’s cancer risk estimates for EO are based entirely on male workers of the NIOSH retrospective study. EPA unfairly rejects the published and peer reviewed UCC study, which also include estimates of exposure for study subjects, as relevant both for assessment of causation and for dose-response assessment. The UCC study (Greenberg *et al.*, 1990; Teta *et al.*, 1993) identified no deaths due to lymphocytic leukemia. EPA speculates that this is due to possible differences in coding of death certificates in West Virginia.⁹ Also, EPA states “. . . none of the leukemia death certificates in the UCC study specified ‘lymphocytic’ leukemia as the histologic type, whereas most of the NIOSH death certificates listed ‘lymphocytic’ leukemia on the death certificate.”¹⁰ Based on this information, EPA incorrectly speculates there were more incomplete death certificates in the UCC study. Instead, the 7 cases of leukemia identified in the

⁸ See Section I.C.2.a (pp. 11-13) of the Panel’s December 8, 2006, comments. See also Section I.D (pp. 65-67) of the Panel’s December 8, 2006, comments regarding EPA’s numerous computational errors that skew results.

⁹ Draft Cancer Assessment at 6.

¹⁰ *Id.* at 121.

Greenberg, *et al.* (1990) UCC study from death certificates were well described: 2 acute myelogenous leukemias, 2 chronic myelogenous leukemias, 1 acute myeloblastic leukemia, 1 myelogenous leukemia, and 1 acute leukemia. The latter non-specific leukemia is the only one that could have been a lymphocytic type of leukemia. Furthermore, Greenberg, *et al.* (1990) reported the consistency of the death certificate diagnosis with a pathology review of medical records for these cases, a validation not conducted for cases in the NIOSH study. In addition to ignoring the absence of increases in females, EPA also is ignoring the uncertainty in the NIOSH findings given the predominance of verified myeloid leukemias and the absence of lymphoid subtypes in the UCC cohort.

EPA challenges consideration of the UCC study in any dose-response assessment by criticizing aspects of the exposure assessment in this study. Because EPA did not understand the different manufacturing processes, it could not interpret the sufficient exposure information and, therefore, concluded incorrectly that the UCC study is invalid and should not be used.

EPA should derive its hazard characterization and cancer risk estimates from the entire body of evidence, rather than solely from the male workers in the NIOSH study. Thus, the Draft Cancer Assessment fails to use a weight-of-evidence approach that relies on *all* relevant information in hazard characterization and derivation of unit risk factors, as required under the Cancer Guidelines, and thus does not provide a sound scientific basis on which to assess potential health risk exposure EO poses.

I.B. EPA Improperly Relies Entirely on the Males in Its Assessment of LH Cancer Mortality

This section addresses, in part, the SAB Charge Questions 1a, d; 2a; and 3.

EPA's LH cancer risk estimates for EO are based entirely on data in males in the NIOSH retrospective study. In this study, increased risks of LH cancer were observed in males but not females, even though the NIOSH cohort was large and diverse, and consisted of more women than men. EPA's exclusive reliance on the male data is scientifically unsound without a mechanistic justification for treating males and females differently with respect to LH, which the analysis lacks. Furthermore, by relying only on data in males, the precision of the estimates is reduced. EPA's cancer risk characterization should include both males and females, consistent with a weight-of-evidence approach that relies on *all* relevant information (*see* Section I.A. above), as required under the Cancer Guidelines.

II. EPA FAILED TO IDENTIFY EO AS BOTH A WEAK MUTAGEN AND WEAK ANIMAL CARCINOGEN

This section addresses, in part, the SAB Charge Questions 1a, d; 2a; and 3.

EO is a DNA-reactive genotoxic agent, as demonstrated by numerous *in vitro* and *in vivo* studies (descriptions and references provided in the Panel's December 8, 2006, comments to EPA). It is, however, only weakly mutagenic, even though the large number of positive tests have erroneously led to a suggestion to the contrary (Waters *et al.*, 1998). Critical analysis of the genetic activity profile of EO, taken from IARC Monograph 60 and Waters, *et al.* (1998), reveals

that the average lowest effective exposure concentration in the *in vitro* mutagenicity tests that have produced positive results were greater than 1.0 µg/ml -- and often closer to 10.0 µg/ml. Based on dosimetry analysis in the mouse, achieving even the lower level in blood would require an inhalation exposure of greater than 150 parts per million (ppm) for four hours (Brown *et al.*, 1998). This is consistent with results of *in vivo* mutagenicity studies in mice and rats, where low physiologically administered EO exposure levels (<10.0 ppm) have often shown minimal to no mutational effects over background, at either the gene or chromosome level. Molecular epidemiological studies in humans, also evaluating gene and/or chromosome level mutational changes, have revealed EO exposure concentrations below which no effects over background are observed (descriptions and numerous references to experimental animal and human observational studies also provided in the Panel's December 8, 2006, comments to EPA). Although cytogenetic changes in humans exposed to EO were instrumental in classifying EO as a human carcinogen, a critical review of the studies on which this judgment was based has concluded that EO exposure levels in the range of 20-25 ppm are required to convincingly produce chromosome aberrations in the peripheral blood lymphocytes of humans (Preston, 1999).

Weak mutagenicity is to be expected for a naturally produced metabolite such as EO, where homeostatic mechanisms for protection against the production of mutations have had to develop. For EO, the most effective of these homeostatic mechanisms appears to be DNA repair, as shown by mechanistic studies in *Drosophila* that have evaluated mutagenic potency in male germ cells (Vogel and Nivard, 1998; Nivard *et al.*, 2003). The *Drosophila* system is particularly sensitive, and allows for assessment of the importance of DNA repair by selective matings of treated males to females that are either proficient or deficient in DNA repair. DNA repair is essentially absent in post-meiotic male germ cells (all species). The chemical lesions (adducts) produced in these cells are processed to mutations, scored in the offspring, only if they remain unrepaired until the initial wave of post-fertilization DNA synthesis in the ovum.

Mutagenic agents can be classified as to their male germ cell stage specificity, with weak mutagens being stage-specific in that they induce heritable mutations preferentially, or only, in post-meiotic male germ cells (where intrinsic repair is absent). Stage-specific chemical mutagens are weak mutagens with the above cited studies demonstrating that effective repair is the reason for this. EO is a stage-specific mutagen, and was among the weakest in a group of 41 alkylating agents evaluated for mutagenic and carcinogenic potency (Vogel *et al.*, 1998). This has particular relevance for estimation of carcinogenicity, as shown by an analysis of 26 of these agents, with sufficient information in the International Agency for Research on Cancer (IARC) database for analysis. This analysis, which included EO, revealed a remarkable relationship between carcinogenic potency, acute toxicity, and germ cell specificity (Figure 12, Vogel *et al.*, 1998). The germ cell-specific alkylating agents as a group were characterized as having the lowest carcinogenic potency. Among these weak mutagens, EO showed the second lowest carcinogenic potency in the analysis, with only propylene oxide scoring lower.

The correlation of an agent's mutagenic potency with its carcinogenic potency is to be expected for a chemical that exerts its carcinogenic effect through a genotoxic mode of action. If genotoxicity is the means by which a chemical induces cancer, it follows that it will not induce a cancer under conditions where it does not induce mutations, at either the chromosome or gene level, thus providing a mechanistic basis for estimating carcinogenicity.

Importantly, the 10 ppm concentration level, which was the lowest concentration tested, produced a non-statistical increase in this tumor type, and only in females. This is the level below which minimal to no mutagenic changes are observed in rodents exposed to EO by physiological means. Previous assessments of EO inhalation time to tumor in rats showed an absence of increased cancer risk below 10 ppm.¹¹ These data showed that the increased risks observed at higher experimental doses did not extend to the lowest experimental dose. Although the human epidemiological data are paramount for the quantitative risk assessment of EO, to comply with the Cancer Guidelines, EPA should include this and other relevant animal data in its weight-of-evidence characterization of EO.

III. EPA'S RISK ESTIMATES DO NOT PASS SIMPLE REALITY CHECKS

This section addresses, in part, the SAB Charge Questions 1a; 2b; and 3.

III.A. The Results of the Draft Cancer Assessment Are at Odds with the Results of Assessments EPA Has Undertaken for Other Substances That Are Considered Potent Mutagens and/or Potent Carcinogens

The Draft Cancer Assessment wrongly posits that the risk of developing cancer from EO exposure is 50x more potent than EPA's recent value for butadiene, 330x the risk from exposure to vinyl chloride, and 640x the risk from exposure to benzene (*see* Table 1). Yet, EO is a *weak* mutagen and animal carcinogen and the epidemiological evidence of carcinogenicity is limited.

¹¹ Appendix C. Implications of the Time-to-Response Information in Hazard Assessment of Ethylene Oxide by Leon Golberg, CRC Press Inc., 1986.

Table 1 -- Negligible Risk [Risk Level E-6 or 1 in 1,000,000]¹²

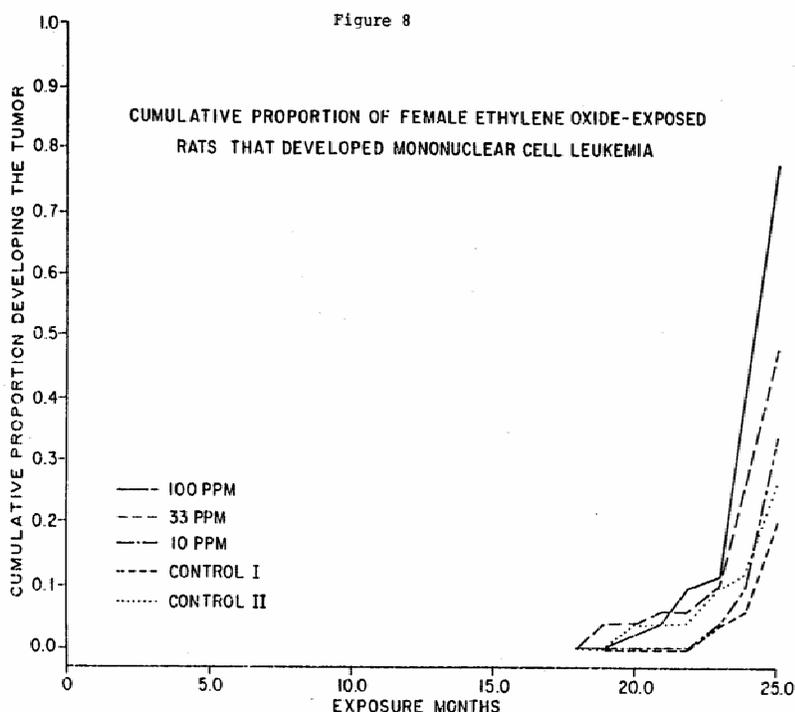
Chemical	<i>De minimis</i> Concentration (µg/m³)	<i>De minimis</i> Concentration (µg/m³)	Ratio to EO
Acetaldehyde	5.0x10 ⁻¹	0.5	710x
Benzene	4.5x10 ⁻¹	0.45	640x
Propylene oxide	3.0x10 ⁻¹	0.30	430x
2,4,6-Trichlorophenol	3.0x10 ⁻¹	0.30	430x
Vinyl chloride	2.3x10 ⁻¹	0.23	330x
Formaldehyde	8.0x10 ⁻²	0.08	110x
Carbon tetrachloride	7.0x10 ⁻²	0.07	100x
1,1,2,-Trichloroethane	6.0x10 ⁻²	0.06	86x
1,3-Butadiene (old?)	3.0x10 ⁻²	0.03	43x
PCBs	1.0x10 ⁻²	0.01	14x
1,2-Diphenylhydrazine	5.0x10 ⁻³	0.005	7x
Toxaphene	3.0x10 ⁻³	0.003	4x
N-Nitrosopyrrolidine	2.0x10 ⁻³	0.002	3x
Heptachlor	8.0x10 ⁻⁴	0.0008	1
Ethylene Oxide (EO)	7.0x10⁻⁴	0.0007	1

III. B. The Results of the Draft Cancer Assessment Are at Odds with EPA's Conclusion That EO Is a Potent (*De Minimis* Level < 1 ppt) Human Carcinogen and EO's Potency Seen in Animal Studies

Section I.C of these comments provides clear support for EO's weak mutagenicity. The Figure below displays plainly that EO is not an example of a potent carcinogen, and thus provides further evidence of EO's weak mutagenicity. Tumors were not

¹² This Table contains figures available at <http://www.epa.gov/iris/>.

increased at the 18-month sacrifice at any exposure level, up to 100 ppm, and leukemia incidence did not increase until the 23rd month of exposure.¹³



III.C. The Draft Cancer Assessment Grossly Over Predicts the Observed Number of Cancer Mortalities by More Than 60-Fold

EPA's Draft Cancer Assessment grossly over predicts the observed number of responses in the NIOSH study, the study upon which EPA's analyses were based. Steenland, *et al.* (2004) reports 37 observed LH cancer mortalities in the 7,645 male workers with exposure data. Table 4 in Steenland, *et al.* (2004) implies that the corresponding expected number of LH cancer mortalities is approximately 35. Thus, Steenland, *et al.* (2004) noted an excess of approximately 2 LH cancer deaths over what was expected.

In the NIOSH data made available to the Panel, there were 37 LH cancer mortalities in the 7,634 male workers with exposure data and known birth dates. Using the NIOSH data and the 1990 U.S. male age-dependent background rates for LH cancer mortality, the expected number of LH cancer mortalities is 34.4 among these 7,634 workers if none of these workers had been exposed to EO. The observed excess of 2.6 (*i.e.*, 37-34.4) LH cancer

¹³ See Sielken, R. in "A Time to Response Perspective on Ethylene Oxide's Carcinogenicity," in Paustenbach, D. ed. The Risk Assessment of Environmental and Human Health Hazards: A textbook of case studies. Wiley Interscience (1989).

mortalities is comparable to the excess of 2 LH cancer mortalities Steenland, *et al.* (2004) reported for 7,645 workers.

Using the same 7,634 workers in the NIOSH data and the same 1990 U.S. male age-dependent background rates for LH cancer mortality, the expected number of LH cancer mortalities would be 197.8 if EPA's slope factor of 0.000347 per ppm-day were used (that is, if the age-dependent background rate for LH cancer mortality in each worker's person-years were multiplied by $(1 + 0.000347 \times \text{worker's cumulative ppm-days by that person-year})$). Thus, using EPA's slope factor of 0.000347 per ppm-day, approximately 197.8 LH cancer mortalities should have been observed. Because only 37 were observed, EPA's slope factor is plainly overpredictive by more than 160 LH cancer mortalities. Furthermore, comparing the observed excess of 2.6 (*i.e.*, 37-34.4) to the excess 163.4 (*i.e.*, 197.8-34.4) predicted using EPA's slope factor of 0.000347 per ppm-day overpredicts the excess LH cancer mortalities by more than 60-fold (*i.e.*, $163.4/2.6 = 62.8$).

Analogously, if EPA's preferred 95% upper confidence limit (UCL) on the slope of 0.000760 per ppm-day were used, then EPA's predicted number of LH cancer mortalities would be 334.7. Comparing the observed excess of 2.6 to the excess 300.3 (*i.e.*, 334.7-34.4) predicted using EPA's slope factor of 0.000760 per ppm-day, EPA's 95% UCL on the slope of 0.000760 per ppm-day overpredicts the excess LH cancer mortalities by more than 100-fold (*i.e.*, $300.3/2.6 = 115.5$). Based on the foregoing, it is clear that EPA's analysis grossly overstates potential risk EO exposure poses.

III.D. EPA's Draft Unit Risk Values for EO Are Not Applicable to the General Public

EPA's unit risk value for EO is based upon epidemiology data for LH cancer mortality in male workers from the NIOSH cohort. Two additional data sets that EPA should consider including in its assessment are: (1) female workers from the NIOSH cohort mortality study (Steenland *et al.*, 2004); and (2) male workers from the UCC cohort (Teta *et al.*, 1993). The NIOSH female and UCC male data could be used as validation data sets for the unit risk value derived from the NIOSH male data in which the resulting unit risk value is used to predict the response and comparisons are made to observed response. Regarding this approach, because it is clear that EPA's unit risk value for EO overestimates by orders of magnitude the observed number of LH deaths in NIOSH males (in which excess deaths were observed), it is expected that EPA's unit risk value will overestimate the observed number of LH deaths in NIOSH females and UCC males (in which excess deaths were not observed) by an even greater margin. Accordingly, EPA's unit risk value cannot be used to estimate the potential risks to the general public from EO exposure with any reasonable degree of confidence.

III.E. The 1×10^{-6} *De Minimis* Risk-Based Concentrations Calculated from EPA's Draft Unit Risk Values for EO of 0.00036 ppb Are One to Several Orders of Magnitude Below Ambient Concentrations and Concentrations Corresponding to Endogenous Production in Humans

A comparative analysis of background and internal body levels of EO shows that the 1×10^{-6} risk-based concentrations calculated from EPA's draft unit risk values for EO are one to several orders of magnitude *below* ambient concentrations and concentrations corresponding to endogenous production.

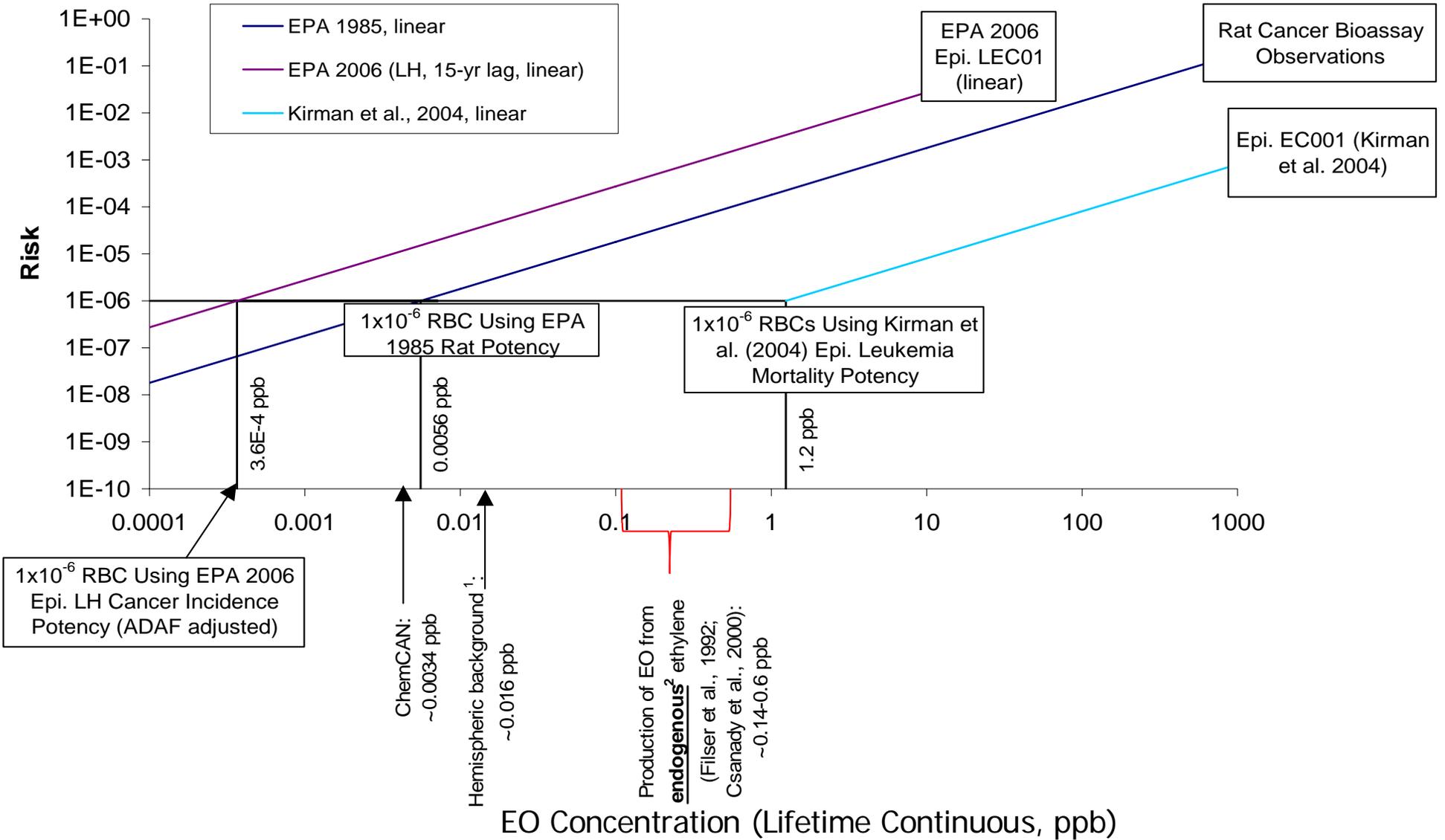
Estimates of concentrations of EO in air in the 48 contiguous United States, derived from atmospheric dispersion modeling and U.S. emission inventories, are available (Woodruff *et al.*, 1998). Mean concentrations predicted for 1990 in Michigan and New York, which border southern Ontario, were 0.0027 and 0.0033 parts per billion (ppb), respectively. When the average of these concentrations was assumed for the concentration of EO in air advected into southern Ontario, the concentrations a Level 3 fugacity model (CHEMCAN) predicted were approximately 0.0034 ppb EO for southern Ontario (WHO, 2003), 10 times higher than the EPA proposed *de minimis* value of 0.00036 ppb.

In 1987, the California Air Resources Board designated EO as a toxic air contaminant and began monitoring ambient background concentrations as part of determining the necessity of promulgating an emissions control measure. Existing measurement methods, however, lacked the sensitivity for detecting low background concentrations of EO (expected to be in the parts per trillion (ppt) range). A study was performed to develop and demonstrate the efficacy of a new sampling and analytic method (Havlicek *et al.*, 1992). The investigator successfully developed a gas chromatography/ion-trap mass spectrometry method for analysis of ambient air samples. For source testing, the investigator developed a method of analysis using portable gas chromatography with photoionization detection. The methods were tested at several locations around the state: near process operations, in urban areas, and in remote coastal areas. In addition, the investigator and staff from state and local regulatory agencies collaborated to develop methods to monitor EO emissions from hospital sterilizer facilities. The lowest ambient EO concentration found was 0.016 ppb at remote coastal locations, about 50 times higher than the EPA proposed *de minimis* value of 0.00036 ppb.

EO is produced within the body by the epoxidation of endogenous ethylene. Humans and rats produce ethylene at rates of 0.471 and 11.2 nmol/hr-kg body weight, respectively (Csanady *et al.*, 2000). Background levels of EO in human blood are predicted to be approximately 0.04 nmol/L by Csanady, *et al.* (2000) to up to approximately 4-fold higher (0.16 nmol/L) by Filser, *et al.* (1992). Based upon PBPK simulations, this range of endogenous concentrations of EO is the same as is expected to result from continuous 24-hour exposure to 0.14-0.6 ppb EO that is 400-1700 times greater than the EPA proposed *de minimis* value of 0.00036 ppb.

The 1×10^{-6} risk-based concentrations for EO in air are presented below in Figure 2 and compared to ambient concentrations of EO (labels indicated below the x-axis) and concentration ranges corresponding to production from endogenous ethylene.

Figure 2.



¹Natural EO produced by plants, microorganisms, water-logged soil.

²Endogenous ethylene normally produced from lipid peroxidation, oxidation of hemoglobin and methionine, and metabolism by intestinal bacteria

Figure 2 shows clearly that EPA's draft cancer unit risk values for EO are not reasonable. EPA must reexamine the reasonableness of its unit risk values for EO using the best available scientific information. Furthermore, EPA must consider that restricting external exposures to EO below approximately 1 ppb will have little impact on the internal dose of EO due to its production from endogenous ethylene within the body, and therefore would result in negligible or no impact on potential human health risk.

IV. ADDITIONAL ANALYSES ILLUSTRATE THE OVERLY CONSERVATIVE NATURE OF EPA POLICY DECISIONS

This section addresses, in part, the SAB Charge Questions 1a; 2c; and 3.

In addition to EPA's failure to use the underlying NIOSH data and the invalid methodology for dose-response assessment, EPA unjustifiably departed from past risk assessment decisions that enlarge greatly the inherent conservatism in the risk estimates. The SAB should review and ultimately reject these decisions. These include, among others: (1) EPA's reliance on the lower bound of the point of departure (POD), rather than the best estimate when using human data; (2) use of background incidence rates with mortality-based relative rates rather than mortality background rates; (3) EPA's assumption of an 85-year lifetime of exposure, rather than the more traditional 70-year lifetime; and (4) scientifically unjustified default adjustment for early-life exposures. Each of these issues is discussed below, and their adverse impacts are illustrated by comparing EPA's values with values from Poisson regression analyses using the individual subject data in the NIOSH study. In these Poisson analyses, the EPA approach of using LH cancers among males as a response and four quartiles of cumulative EO ppm-days as the exposure metric were employed.

IV.A. The Lower Bound on the POD Is Two to Three Times Less Than the "Best Estimate"; EPA Also Fails to Provide the Central Estimate of Human Health Risk As Well As Appropriate Upper-Bound and Lower-Bound Risk Estimates, Which Is Required by the Cancer Guidelines

Tables 7, 9, 14, and 15, and the corresponding discussions in the text of EPA's Draft Cancer Assessment, present estimates for the EC_{01} , LEC_{01} , and unit risk (calculated as $0.01/LEC_{01}$). In past assessments, EPA has relied upon the central tendency estimates of cancer potency when using human data.¹⁴ By focusing the Draft Cancer Assessment upon the LEC_{01} value instead of the EC_{01} value, the resulting unit risk value is approximately 65-120% higher than if it were based upon the EC_{01} value. In keeping with EPA's Risk Characterization Handbook (EPA, 2000), in which consistency is identified as one of the four desired properties of a successful risk characterization (Transparency, Clarity, Consistency, and Reasonableness or TCCR), the unit risk value derived for EO is not consistent with unit risk values EPA derived previously for other chemicals using human data.

¹⁴ See, e.g., EPA (2002) at 10-20 (noting EPA "has historically used MLEs [maximum likelihood estimates] for cancer risk estimates from human data rather than upper bounds as used with animal data").

More recently, EPA's Cancer Guidelines state, "risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decisionmakers."¹⁵ Similarly, as noted above, EPA must present "the expected risk or central estimate of human health risk," as well as "each appropriate upper-bound or lower-bound estimate of risk." Use of the lower bound on the POD results in a 2- to 3-fold overestimate of risk compared to using central estimate (maximum likelihood estimate).¹⁶

IV.B Using Background Incidence Rates with Mortality-Based Relative Rates Relies on an Unsupported Assumption and Demonstrated Potential to Create Biased Results

EPA's Draft Cancer Assessment employs a methodological change to the calculation of excess lifetime risk for the broad category of LH cancers, despite EPA's recognition of the "potentially problematic" key assumption and potential bias associated with this procedure.¹⁷

Incidence rates are based on those who are diagnosed with the disease, whether they survive or not, while mortality rates only include those who are diagnosed and die from the disease. Application of background incidence rates to the excess lifetime risk calculation, which are greater than mortality rates, will always result in greater lifetime risk, but less so for more fatal diseases. Because cell type is typically unavailable in cohort studies where leukemia or lymphoma incidence is increased, the assumption is typically made that the putative carcinogen causes all forms of these diseases equally in a trade-off to increase sample size. This assumption becomes particularly important if background incidence rates, rather than mortality rates, for all leukemia combined are applied in lifetime risk calculations. It then becomes important as to whether the agent causes a more or less fatal form of these cancers.

In a 2004 publication, Teta, *et al.* examined the validity of using background incidence rates with cohort mortality-based potency estimates to calculate excess lifetime risk. The Teta, *et al.* (2004) analyses, assuming equal exposure-response relationships, demonstrated that when the exposure of interest is not related to all cell types of leukemia equally, this procedure: (1) can introduce measurable bias, the direction of which depends on cell type survival and the slope (potency) of the exposure-response curve; and (2) that the bias may be enhanced with potency adjustments for early-life exposures. The magnitude of under and over estimation for leukemia was found to range from an underestimation of 60% to an overestimation of 20%. This novel approach should not be implemented, given that EPA has now applied this methodology to an even broader category of diseases, has not tested the assumption of similar exposure-response relationships for incidence and mortality, and recognizes the potential for bias of unknown direction.

¹⁵ Cancer Guidelines at 3-17.

¹⁶ *Id.* ("...it may be appropriate to emphasize the central estimate in activities that involve formal uncertainty analysis ... as well as ranking agents as to their carcinogenic hazard.").

¹⁷ Draft Cancer Assessment at 35.

IV.C. EPA Inappropriately Extended the Analysis to an Assumed 85-Year Lifetime of Exposure and Cumulative Risk, Rather Than the More Traditional 70-Year Lifetime

EPA-calculated lifetime extra cancer incidence and mortality risk estimates assume 85 years of exposure rather than the typical, conservative assumption of 70 years exposure. EPA's unjustified and unexplained departure from well-established past practice adds further uncertainty and conservatism into the excess lifetime cancer risk estimates for EO.

As noted below, there are several reasons for EPA to reverse its decision to compute lifetime excess cancer risks up to age 85 instead of EPA's standard practice of calculating excess cancer risks up to age 70.

- EPA's standard risk assessment methodology already has many layers of conservatism, such that EPA's approach as a whole, including the standard use of 70 years exposure, has always been considered sufficiently conservative to produce an upper-bound estimate of potential excess cancer risk.
- It is unrealistic to assume that a person spends his or her entire lifetime in the same place with the same ambient exposures. Thus, assuming 70 years of continuous exposure already is a highly conservative if not extreme approach.
- EPA's departure from its typical practice of using 70 years, without explanation, contravenes one of the core values in EPA's Risk Characterization Handbook (EPA, 2000), in which consistency is a hallmark of a successful risk characterization. The National Center for Environmental Assessment's choice makes comparisons between EO and other compounds difficult to make, and it biases the comparison in the direction of an artificially higher risk ranking for EO.
- Available cancer incidence and mortality data are less stable for older age groups. Consequently, EPA has introduced additional uncertainty into the excess lifetime risk estimate.¹⁸

¹⁸ Because the population size decreases at older ages, there is less precision or more variability in estimates of rates (both mortality and incidence). The 95% confidence intervals are twice as wide for the 81-85 age group, compared to the 65-69 age group. This statement is based on mortality and incidence rate information found in the following SEER reports: SEER (2003). SEER*Stat Database: Incidence -- SEER 9 Regs, Nov 2002 Sub (1973-2000), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Surveillance, Epidemiology, and End Results Program; SEER (2003). SEER*Stat Database: Mortality -- All COD, Public-Use With State, Total U.S. (1969-2000), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

- EPA's inexplicable departure from well-established practice with no explanation or justification is a violation of the Administrative Procedure Act and is arbitrary and capricious.

Finally, the dose-response modeling employed in the excess risk calculations is based on data for persons who were not generally followed up to age 85 and persons who were not exposed for 85 years. Thus, the excess risk calculation based on an 85-year lifetime is based on an extrapolation of a dose-response model that has not been shown to apply to an 85-year lifetime. Table 2 shows the distributions of the age at the start of employment, at the end of employment, and at the end of follow-up. Approximately 96% of the workers had ceased new exposures by age 70 years and only 13% of the workers were observed at age 75 or greater.

Table 2 -- Distributions of the age of workers in the NIOSH Mortality Study at the start of employment, end of employment, and end of follow-up (age at death or 1998) (the workers in the Poisson regression analyses; that is, 7,634 male workers in plants with exposure estimates)

Age	Start of Employment			End of Employment			End of Follow-up		
	# of Workers	%	% ≥ Age	# of Workers	%	% ≥ Age	# of Workers	%	% ≥ Age
0 to 20	1688	22.11	100.00	527	6.90	100.00	21	0.28	100.00
25	2220	29.08	77.89	1642	21.51	93.10	73	0.96	99.72
30	1203	15.76	48.81	1141	14.95	71.59	60	0.79	98.77
35	760	9.96	33.05	825	10.81	56.64	93	1.22	97.98
40	556	7.28	23.09	697	9.13	45.83	467	6.12	96.76
45	495	6.48	15.81	657	8.61	36.70	1012	13.26	90.65
50	336	4.40	9.33	509	6.67	28.10	1419	18.59	77.39
55	242	3.17	4.93	438	5.74	21.43	1302	17.06	58.80
60	112	1.47	1.76	406	5.32	15.69	963	12.61	41.75
65	19	0.25	0.29	531	6.96	10.37	694	9.09	29.13
70	3	0.04	0.04	247	3.24	3.42	558	7.31	20.04
75	0	0.00	0.00	11	0.14	0.18	456	5.97	12.73
80	0	0.00	0.00	2	0.03	0.04	281	3.68	6.76
85	0	0.00	0.00	0	0.00	0.01	158	2.07	3.08
> 85	0	0.00	0.00	1	0.01	0.01	77	1.01	1.01
Sum	7634			7634			7634		

Because the background rates of LH cancer mortalities are much greater at older ages than younger ages, the excess risks are more heavily impacted by the years at older ages than the years at younger ages. Thus, using an 85-year lifetime in the excess risk calculations greatly skews the dose-response model at the ages at which the dose-response model is least validated. Calculating excess risks for 70-year lifetimes would lessen this problem. The impact of this choice is an increase in the lifetime excess risk estimate of approximately 3-fold, thus greatly overstating the potential risk EO exposures pose.

EPA's definition of lifetime is internally and externally inconsistent. Within the Draft Cancer Assessment, EPA defines lifetime as 85 years within the context of lifetable

analysis.¹⁹ When calculating the Age-Dependent Adjustment Factor (ADAF) value, however, EPA assumes a lifetime of 70 years.²⁰ This is further complicated by the fact that EPA's Exposure Factors Handbook (EPA, 1997) states that the recommended value for lifetime duration is 75 years, which would be incompatible with a unit risk value derived using 70 or 85 years in the lifetable analysis. EPA needs to define lifetime consistently.

IV.D EPA Should Not Use a Default Adjustment for Early-Life Exposures Because, For EO, It Is Scientifically Unjustified

EPA calculates the additional risk posed by early-life exposure to EO because, according to EPA, there is a lack of "chemical-specific data to evaluate the differences . . . [in] susceptibility."²¹ Despite EPA's assertions, specific, relevant data demonstrate that EPA's application of additional risk estimates for early-life exposures is scientifically unjustified.

Few chemicals have direct data available that can be used to examine the impact of age at first exposure on long-term cancer risk. EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* states that, in the absence of chemical- and age-specific data on exposure and toxicity, mode of action and other relevant studies should be used to determine if age-related differences exist (EPA, 2005). Specifically, EPA recommends describing the mode of action for carcinogenesis, identifying the key biological and toxicological events in that mode of action that are likely to be affected by age, and integrating data on age-related differences in those key events into the risk assessment. In the absence of relevant data to demonstrate differences between children and adults, EPA has recommended that standard adjustment factors should be used for chemicals with a mutagenic mode of action.

In the Draft Cancer Assessment, relevant data related to whether greater risk is associated with early-life exposures were not considered and the default adjustment factors were automatically incorporated into the excess lifetime risk calculations. For example, in the Draft Cancer Assessment, EPA applied an ADAF using default adjustments of 10, 3, and 1 for the age periods of 0-2 years, 2-16 years, and 16-70 years, respectively.²² Consideration of both toxicodynamic and toxicokinetic factors are important in assessing potential differences in increased risk between early and later life exposures.

EPA's use of the default adjustment factors is not justified because there are published data in the epidemiologic and toxicologic literature related to relevant toxicodynamic and toxicokinetic differences that show:

- Children exposed to other alkylating agents are *not* at greater increased risk than adults to leukemia or NHL. In fact, the data suggest that they may be at lower risk. This finding is consistent with the low background rate of acute myeloid leukemia (AML) and NHL in children (Valagussa *et al.*, 1986; Pedersen-Bjergaard *et al.*, 1987; Tucker *et al.*, 1988; van

¹⁹ Draft Cancer Assessment at 59.

²⁰ *Id.* at 57.

²¹ *Id.*

²² *Id.*

Leeuwen *et al.*, 1989; Sankila *et al.*, 1996; Bhatia *et al.*, 2003; Pui *et al.*, 1990; Beaty *et al.*, 1995; Swerdlow *et al.*, 1992; Metayer *et al.*, 2000; Levine and Bloomfield, 1992; Pyatt *et al.*, 2005).

- The pattern of results is consistent with the finding that, in general, children tolerated at least as high a dose of chemotherapeutic alkylating agents tested in Phase 1 trials as adults did (Glaubiger *et al.*, 1982; Marsoni *et al.*, 1985; Carlson *et al.*, 1996). Children also recover more quickly from severe aplastic anemia and stem cell transplantations than adults do, which is believed to be due, in part, to a greater ability to repair damage to the hematopoietic system (Trigg, 2004).
- Animal studies suggest lower endogenous ethylene levels in children, who also have lower levels of the enzyme that oxidizes ethylene to EO (Beckman and Ames, 1998; Pratico, 2002; Sagai and Ichinose, 1980; Lieberman and Kunishi, 1965; Fu *et al.*, 1979; Johsrud, 2003; Ginsberg *et al.*, 2004; Edginton *et al.*, 2006).
- Although limited data suggest that epoxide hydrolase is marginally lower in neonates and young children than in adults (Ginsberg *et al.*, 2004; Omiecinski *et al.*, 1994; Ratanasavanh *et al.*, 1991; Hassett *et al.*, 1997) the impact on body burden would be well below the EPA default.
- Children appear to have a lower body burden of EO based on *N*-(2-hydroxyethyl)valine (HEV) adducts, the relevant biomarker of EO exposure (Bono *et al.*, 2005; Wu *et al.*, 2004; Csanady *et al.*, 2000).
- Lifetime animal bioassays initiated at eight weeks old have not reported a shorter time-to-tumor following chronic EO exposure (Snellings *et al.*, 1984; NTP, 1987).

The cumulative evidence demonstrates that children exposed to alkylating agents are not at greater risk than adults for leukemia or NHL as second primary cancers. Thus, EPA should not use a default adjustment for early-life exposures.

CONCLUSION

The Ethylene Oxide/Ethylene Glycols Panel appreciates the opportunity to comment on the Draft Cancer Assessment. The Panel urges the SAB to peer review the Draft Cancer Assessment thoroughly to ensure the final document reflects the best available science and comports with all requisite EPA guidance documents.

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Appendix A

Sections of the EO Panel's December 8, 2006, Comments That Respond to SAB's Charge Questions

Issue 1: Carcinogenic Hazard

<u>SAB's Charge Questions</u>	<u>Sections of the EO Panel's Comments that Address the SAB's Charge Questions</u>
1. Do the available data and discussion in the draft document support the hazard conclusion that EO is carcinogenic to humans based on the weight-of-evidence descriptors in EPA's 2005 <i>Guidelines for Carcinogen Risk Assessment</i> ?	I.C.1 (pp. 6-10), 4-6 (pp. 31-55)
a. Does the draft document provide sufficient description of the studies, balanced treatment of positive and negative results, and a rigorous and transparent analysis of the data used to assess the carcinogenic hazard of ethylene oxide (EO) to humans?	I.C.1 (pp. 6-10), 5-6 (pp. 32-55)
Does the body of epidemiological data reviewed correctly state the consistency of the findings, including the significance of differences in results using different exposure metrics?	I.C.1-2 (pp. 6-21), 4 (pp. 31-32)
Does the body of epidemiological data reviewed correctly state the utility of the internal (based on exposure category) versus external (<i>e.g.</i> , SMR and SIR) comparisons of cancer rates?	Not Addressed
Does the body of epidemiological data reviewed correctly state the magnitude of the risks and the strength of the epidemiological evidence?	I.C.1-4 (pp. 6-32), 7 (pp. 55-65); I.D (pp. 65-68)
b. Are there additional key published studies or publicly available scientific reports that are missing from the draft document and that might be useful for the discussion of the carcinogenic hazard of EO?	I.C.3 (pp. 21-31), 6 (pp. 32-55)
c. Do the available data and discussion in the draft document support the mode of action conclusions?	I.C.6 (pp. 32-55)
d. Does the hazard characterization discussion for EO provide a scientifically-	I.C.1 (pp. 6-10), 4-6 (pp. 31-55)

balanced and sound description that synthesizes the human, laboratory animal, and supporting (<i>e.g., in vitro</i>) evidence for human carcinogenic hazard?	
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Issue 2: Risk Estimation

<u>SAB's Charge Questions</u>	<u>Sections of the EO Panel's Comments that Address the SAB's Charge Questions</u>
<p>2. Do the available data and discussion in the draft document support the approaches taken by EPA in its derivation of cancer risk estimates for EO? In your response, please include consideration of the following:</p> <p>a. EPA concluded that the epidemiological evidence alone was strong but less than completely conclusive (although EPA characterized the total evidence - from human, laboratory animal, and <i>in vitro</i> studies - as supporting a conclusion that EO as "carcinogenic to humans"). Is the use of epidemiological data, in particular the Steenland, <i>et al.</i> (2003, 2004) data set, the most appropriate for estimating the magnitude of the carcinogenic risk to humans from environmental EO exposures? Are the scientific justifications for using this data set transparently described?</p>	I.C.1 (pp. 6-10), 4 (pp. 31-32), 6 (pp. 32-55)
<p>Is the basis for selecting the Steenland, <i>et al.</i> data over other available data (<i>e.g.,</i> the Union Carbide data) for quantifying risk adequately described?</p>	I.C.1 (pp. 6-10)
<p>b. Assuming that Steenland, <i>et al.</i>, (2003, 2004) is the most appropriate data set, is the use of a linear regression model fit to Steenland <i>et al.</i>'s categorical results for all lymphohematopoietic cancer in males in only the lower exposure groups scientifically and statistically appropriate for estimating potential human risk at the lower end of the observable range?</p>	I.C.1-2 (pp. 6-21), 4 (pp. 31-32); I.D.1 (pp. 65-66)
<p>Is the use of the grouping of all</p>	I.C.2.d (pp. 17-20)

lymphohematopoietic cancer for the purpose of estimating risk appropriate? Are there other appropriate analytical approaches that should be considered for estimating potential risk in the lower end of the observable range?	
Is EPA's choice of a preferred model adequately supported and justified? In particular, has EPA adequately explained its reasons for not using a quadratic model approach such as that of Kirman <i>et al.</i> (2004) based?	I.C.1-2 (pp. 6-21), 4 (pp. 31-32), 7 (pp. 55-65)
What recommendations would you make regarding low-dose extrapolation below the observed range?	Not addressed
c. Is the incorporation of age-dependent adjustment factors in the lifetime cancer unit risk estimate, in accordance with EPA's Supplemental Guidance (U.S. 2005b), appropriate and transparently described?	I.C.3.d (pp.29-31); I.D.3 (67-68)
d. Is the use of different models for estimation of potential carcinogenic risk to humans from the higher exposure levels more typical of occupational exposures (versus the lower exposure levels typical of environmental exposures) appropriate and transparently described in Section 4.5?	I.C.2.e (20-21)
e. Are the methodologies used to estimate the carcinogenic risk based on rodent data appropriate and transparently described? Is the use of "ppm equivalence" adequate for interspecies scaling of EO exposures from the rodent data to humans?	I.C.5 (p. 32) ; I.D.2 (pp. 66-67)

Issue 3: Uncertainty

<u>SAB's Charge Questions</u>	<u>Sections of the EO Panel's Comments that Address the SAB's Charge Questions</u>
3. EPA's Risk Characterization Handbook requires that assessments address in a transparent manner a number of important factors. Please comment on how well this assessment clearly describes, characterizes and communicates the following: a. the assessment approach employed?	Uncertainty, in general, is addressed in the context of sections I.C.1-7 (pp. 66-65).

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| <ul style="list-style-type: none">b. the assumptions and their impact on the assessment;c. the use of extrapolations and their impact on the assessment;d. plausible alternatives and the choices made among those alternatives;e. the impact of one choice versus another on the assessment;f. significant data gaps and their implications for the assessment;g. the scientific conclusions identified separately from default assumptions and policy calls;h. the major risk conclusions and the assessor's confidence and uncertainties in them, and;i. the relative strength of each risk assessment component and its impact on the overall assessment. | |
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**Sections of the EO Panel's December 8, 2006, Comments That Address the Panel's
Additional Charge Questions**

<u>The EO Panel's Additional Charge Questions</u>	<u>Sections of the EO Panel's Comments that Address the Additional Charge Questions</u>
Is the unit risk factor calculated in this assessment reasonably consistent with the mutagenic potency of EO and with regard to the relative risks that can be derived from the body of epidemiology studies?	I.C.1a (pp. 7-10), 6- 7 (pp. 32-55)
Is the unit risk estimate realistic given endogenous levels of EO that are produced naturally in humans?	I.C.6-7 (pp. 32-55)
Has EPA presented its conclusions about the carcinogenic risk from EO exposure in a public health context that is both understandable and useful to decision makers? Specifically, has EPA adequately described the distribution of risk estimates, including lower, central and upper bound risk estimates?	I.C.3.a (pp. 22-23), 7 (pp. 55-65)
How well has EPA characterized the carcinogenicity of EO in light of the requirements specified in the EPA publications, Information Quality Guidelines, EPA's Risk Characterization Handbook, and EPA's Guidelines for Carcinogenic Risk Assessment?	I.A (pp. 3-5)
Have potential risk assessment policy changes such as the use of (1) 85 year lifetime excess cancer risk instead of 70 years; (2) background incidence rates of cancer with mortality-based relative risk estimates; and (3) the lower bound on the point of departure when using human data, been adequately reviewed by SAB?	I.C.3 (pp. 21-31)
How justified are EPA's statistical modeling and analyses decisions, particularly in its epidemiology-based dose-response modeling using only summary surrogate statistics from a publication? Should available data on individual study subjects be used in the analyses?	I.C.1-2 (pp. 6-21)