CHARGE QUESTIONS FOR EPA'S SCIENCE ADVISORY BOARD (SAB) REVIEW OF THE ETHYLENE OXIDE (EtO) CARCINOGENICITY ASSESSMENT

EPA's Office of Research and Development (ORD) has requested that the Science Advisory Board (SAB) review its document entitled "Evaluation of the Carcinogenicity of Ethylene Oxide". This document is EPA's draft of the assessment of the carcinogenicity of ethylene oxide (EtO). The assessment was prepared by the National Center for Environmental Assessment, which is the health risk assessment program in the Office of Research and Development. The assessment broadly supports activities authorized in the 1990 Clean Air Act and is of particular interest to EPA's Office of Air and Radiation. However, this review also should be applicable to the needs of all program Offices and Regions in evaluating the carcinogenicity of EtO.

EPA last published an assessment of the potential carcinogenicity of EtO in 1985 (U.S. EPA, 1985). The current assessment reviews the more recent database on the carcinogenicity of EtO. The scientific literature search for this assessment is generally current through June 2004, although a few later publications are included. This assessment focuses on lifetime cancer risk from inhalation exposure.

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

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

In accordance with EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), EPA characterized EtO as carcinogenic to humans based on the total weight of evidence.

This evidence, as assessed by EPA, included:

a) strong, though less than completely conclusive, evidence of carcinogenicity from human studies
b) sufficient evidence of carcinogenicity in laboratory animals
c) EtO is a direct-acting alkylating agent with clear evidence of mutagenicity/genotoxicity, and there is sufficient evidence that DNA adduct formation and the resulting mutagenic/genotoxic effects are key events in the mode of action of EtO carcinogenicity
d) evidence of chromosome damage in humans exposed to EtO, supporting the inference that the same mode of action for EtO carcinogenicity is operative in humans

This document describes the derivation of inhalation unit risk estimates for cancer mortality and incidence based on the human data. An EC_{01} of 44 µg/m^3 (0.024 ppm) was calculated using a life-table analysis and linear modeling of the categorical Cox regression analysis results for excess lymphohematopoietic cancer mortality in males reported in a high-quality occupational epidemiologic study (Steenland et al., 2004). Linear low-dose extrapolation from the LEC_{01} yielded a lifetime extra cancer mortality unit risk estimate of 5.0×10^{-4} per µg/m^3 (0.92 per ppm) of continuous EtO exposure. Applying the same linear regression coefficient and life-table analysis to background male lymphohematopoietic cancer *incidence* rates yielded an EC_{01} of 24 µg/m^3 (0.013 ppm) and a preferred lifetime extra cancer unit risk estimate of 9.0×10^{-4} per µg/m^3 (1.6 per ppm). The preferred estimate is greater than the estimate of 5.0×10^{-4} per µg/m^3 (0.91 per ppm; EC_{01} = 44 µg/m^3) calculated, using the same approach, from the results of a breast cancer incidence study of the same worker cohort (Steenland et al., 2003), and is recommended as the potency estimate for Agency use.

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

with EPA's Supplemental Guidance.]

Unit risk estimates were also derived from the three chronic rodent bioassays for EtO reported in the literature. These estimates, ranging from 2.2×10^{-5} per µg/m^3 to 4.6×10^{-5} per µg/m^3, are about an order of magnitude lower than the estimates based on human data [unadjusted for early-life susceptibility]. The Agency takes the position that human data, if adequate data are available, provide a more appropriate basis than rodent data for estimating population risks (U.S. EPA, 2005a), primarily because uncertainties in extrapolating quantitative risks from rodents to humans are avoided. Although there is a fairly sizable difference between the rodent- and human-based estimates, the assessment infers that the similarity between the unit risk estimates based on the male lymphohematopoietic cancer and the female breast cancer results increases confidence in the use of the unit risk estimate based on the male lymphohematopoietic cancer results.

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

The SAB Ethylene Oxide Review Panel is being asked to comment on the scientific soundness of this carcinogenicity assessment. The specific charge questions to the Panel are as follows:

Issue 1: Carcinogenic Hazard (Section 3 and Appendix A of the Draft)

1. Do the available data and discussion in the draft document support the hazard conclusion that EtO is carcinogenic to humans based on the weight-of-evidence descriptors in EPA's 2005 *Guidelines for Carcinogen Risk Assessment*? In your response, please include consideration of the following:

1.a. EPA concluded that the epidemiological evidence on EtO carcinogenicity was strong but less than completely conclusive. 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 (EtO) to humans? Please comment on the EPA's characterization of the body of epidemiological data reviewed. Considerations include: a) the consistency of the findings, including the significance of differences in results using different exposure metrics, b) the utility of the internal (based on exposure category) versus external (e.g., SMR and SIR) comparisons of cancer rates, c) the magnitude of the risks, and d) the strength of the epidemiological evidence.

1.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 EtO?

1.c. Do the available data and discussion in the draft document support the mode of action conclusions?

1.d. Does the hazard characterization discussion for EtO provide a scientifically-balanced and sound description that synthesizes the human, laboratory animal, and supporting (e.g., *in vitro*) evidence for human carcinogenic hazard?

Issue 2: Risk Estimation (Section 4 and Appendices C and D)

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 EtO? In your response, please include consideration of the following:

2.a. EPA concluded that the epidemiological evidence alone was strong but less than completely conclusive (although EPA characterized the total evidence, animal and human, as supporting a conclusion that EtO as "carcinogenic to humans"). Is the use of epidemiological data, in particular the Steenland et al. (2003, 2004) data set**,** the most appropriate for estimating the magnitude of the carcinogenic risk to humans from environmental EtO exposures? Are the scientific justifications for using this data set transparently described? Is the basis for selecting the Steenland et al. data over other available data (e.g., the Union Carbide data set) for quantifying risk adequately described?

2.b. Assuming that Steenland et al. (2003, 2004) is the most appropriate data set, is the use of a linear regression model fit to Steenland et al.'s categorical results for all lymphohematopoietic cancer in males in the lower exposure groups scientifically and statistically appropriate for estimating potential human risk at the lower end of the observable range? Is the use of the grouping of all 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 et al (2004)? What recommendations would you make regarding low-dose extrapolation below the observed range?

2.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. EPA, 2005b), appropriate and transparently described?

2.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?

2.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 EtO exposures from the rodent data to humans?

Issue 3: Uncertainty (Sections 3 and 4)

1. EPA's *Risk Characterization Handbook* recommends 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;
b. The use of 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.