ETHYLENE OXIDE

No comments were provided on the **environmental sections** of the CEPA PSL Assessment Report on Ethylene Oxide.

Comments on the **health-related sections** of the CEPA PSL Assessment Report on ethylene oxide were received from Chemstar, Shell Chemical Co., and Union Carbide Corp, on behalf of the Ethylene Oxide Industry Council (EOIC) of the Chemical Manufacturers Association (Arlington, VA, USA). In the submission, it was noted that "*EOIC members account for essentially all U.S. production of ethylene oxide and include a broad spectrum of ethylene oxide users in applications such as sterilizers, ethoxylators, and manufacturers of spices, pharmaceutical, cosmetic, medical, and health products*". (members of the EOIC were Abbott Laboratories; Arc Chemical Corp; BASF Corp; Celanese Ltd; Condea Vista Co; The Dow Chemical Co; Eastman Chemical Co; Honeywell (formerly AlliedSignal, Inc); Huntsman Corp; Lyondell Chemical Co; McCormick & Company Inc; Shell Chemical Co; Sunoco Inc; and Union Carbide Corp).

Responses to individual comments which covered seven major issues are summarized below. With the exception of those related to exposure, all of these comments were raised in several earlier stages by the CMA/EOIC panel. This included provision of comments during first stage review of the health-related supporting documentation for adequacy of coverage and submission to the Chair of the independent panel of scientific experts that reviewed the draft health-related supporting documentation, hazard characterization and exposure-response analyses. Additional documentation on these submissions and responses thereto is available in Health Canada (1999) and Toxicology Excellence for Risk Assessment (1999).

To ensure transparency and defensibility of the health assessments, a cut-off date for consideration of new data is specified. In addition, the process for assessing the risks to human health includes several stages of internal and external review to ensure both quality and transparency. Addition of new data beyond the cut-off date, even if it was certain that these were the only new relevant data, would require an additional round of both internal and external reviews. This is impractical given the legally mandated time limits for completing these assessments. Such data are flagged for consideration in the risk management/strategic options process or a subsequent re-assessment.

Comment	Response
EOIC indicated that based upon its own interpretation of the available epidemiological, experimental carcinogenicity and genotoxicity data, Health Canada's classification of ethylene oxide as being "highly likely	This issue was raised previously by one of the EOIC contributors (M.J. Teta) during first-stage review of the supporting documentation. It was also raised in a submission (M.J. Teta) to the chair of the independent panel of scientific experts that

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carcinogenic to humans", should be revised.	reviewed the draft health–related supporting documentation, hazard characterization and exposure -response analyses. A detailed discussion of the basis for the carcinogenic classification of ethylene oxide is included in the Assessment Report. As agreed by the independent panel of scientific experts, while epidemiological data are inconclusive, the weight of evidence of the biological plausibility of the carcinogenicity of this substance is convincing, based on its genotoxicity, carcinogenicity in experimental animals and the lack of qualitative differences in metabolism between humans and animals. To ensure consistency, weight of evidence determinations for hazard characterization are made by Health Canada against specified criteria, taking into account technical input from external contributors. For ethylene oxide, the weight of all available evidence is considerable and consistent with that for other Priority Substances considered highly likely carcinogenic to humans.
EOIC suggested that Health Canada inappropriately discounted the available epidemiological data on the carcinogenicity of ethylene oxide in its assessment of this substance. EOIC suggested that conclusions regarding the carcinogenicity of ethylene oxide in humans, based upon its carcinogenicity in animals and its genotoxicity, are not supported by the weak evidence of risk in epidemiological investigations.	This issue was raised previously by one of the EOIC contributors (M.J. Teta) during first-stage review of the supporting documentation. It was also raised in a submission (M.J. Teta) to the chair of the independent panel of scientific experts that reviewed the draft supporting documentation, hazard characterization and exposure-response analyses. As indicated in the Assessment Report, the basis for the carcinogenic classification of ethylene oxide rests primarily on the biological plausibility of the carcinogenicity of this substance in animals and humans, its

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	genotoxicity, and the lack of qualitative differences in metabolism between humans and animals, as reviewed and agreed by the independent panel of scientific experts. Data from epidemiological studies are not sufficient to preclude the carcinogenicity of ethylene oxide for purposes of hazard characterization. The comment seems to reflect the reviewers' confidence in the implications of this database for exposure-response, which is not germane to the classification of hazard potential.
EOIC considered that Health Canada used inappropriate and biologically implausible assumptions in the dose-response analysis for carcinogenicity, and in establishing the priority for further action. EOIC suggested that dose-response analysis be conducted with data derived from epidemiological studies, and that an animal cancer model other than the development of mononuclear cell leukemia in rats be employed to estimate carcinogenic potency. EOIC also suggested that different estimated values of exposure be used in the calculation of the Exposure Potency Index (EPI) and provided its own comparison of the consistency between animal- and human-based cancer risk characterization (see response below on exposure estimation).	Issues concerning the analysis of exposure-response were raised previously by one of the EOIC contributors (M.J. Teta) in a submission to the chair of the independent panel of scientific experts that reviewed the draft health-related supporting documentation, hazard characterization and exposure -response analyses. Available data are inadequate as a basis for development of a biologically-based case-specific model for exposure-response for ethylene oxide. As a result, the model chosen was that which best fit the observed data. Uncertainties associated with the carcinogenic potencies derived for this substance are discussed in the report. The independent panel of scientific experts *"…agreed that the animal data are the appropriate basis for developing a quantitative estimate*" of exposure-response. Moreover, Health Canada compared tumorigenic potencies developed based on studies in animals to risks of haematological cancers reported in epidemiological studies in populations occupationally-exposed to ethylene oxide. The results indicated that risks predicted

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	based on the most sensitive outcome in rats were consistent with the confidence intervals of the rates for both leukaemias overall and all haematopoietic neoplasms in males in the only cohort study in which individual cumulative exposure was characterized. However, it was also concluded that the limitations of this comparative exercise preclude its meaningful contribution to quantitation of risk. These include uncertainties of the available epidemiological data on ethylene oxide (i.e., particularly with respect to periods of follow-up in investigations of greatest sensitivity). Moreover, meaningful direct comparison of potency in laboratory animals with that in humans is precarious at best in light of the inadequacy of available information on interspecies variations in kinetics and metabolism and mode of action to serve as a basis for characterization of site concordance between animals and humans. The extremely wide range of the confidence limits on the SMRs in the epidemiological studies also contribute to their limited contribution to quantification of risk. This was discussed and agreed by the independent panel of scientific experts who considered that the significant uncertainties in conducting such comparisons limit their utility, with different approaches supporting different conclusions. With respect to the development of mononuclear cell leukemias in rats, appropriate qualification is included in the Assessment Report. It is reported therein that: "Mononuclear cell leukaemias are unique to the F344 strain of rat. These tumours arise spontaneously, primarily in older animals. The exact etiology of this

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	tumour type including cell of origin has not been definitively identified". However, both Health Canada and the independent panel of scientific experts did not consider this as an adequate basis for lack of inclusion of these tumours in quantification of exposure-response. Uncertainties of the carcinogenic potencies derived on the basis of the dose-response analysis for the development of mononuclear cell leukemias in rats are outlined within the Assessment Report.
EOIC indicated that the discussion of genetic effects should acknowledge the limitations of the genotoxicity data from human monitoring studies on cytogenetic changes in ethylene oxide-exposed workers, and their relevance in predicting carcinogenic risk. In this context, a review article by an individual author (J. Preston) was referenced.	This issue was raised previously by two of the EOIC contributors (M.J. Teta; R. Gingell) during first-stage review of the supporting documentation, and in a submission (M.J. Teta) to the chair of the independent panel of scientific experts that reviewed the draft health-related supporting documentation, hazard characterization and exposure-response analyses. Since carcinogenic risk has not been predicted on the basis of the cytogenetic studies, part of the comment is not relevant. In addition, the Assessment Report includes a full discussion of the weight of evidence of cytogenetic changes in human populations when considered in the context of traditional criteria of causality. Based on this assessment, it is concluded that there is rather consistent evidence in the most sensitive studies that ethylene oxide interacts with the genome of cells within the circulatory system, in occupationally-exposed humans. Indeed, in comparison with that for other substances, the relative consistency of the data across studies is rather striking, though there are some inconsistent observations within studies particularly in relation to the nature of clastogenic effects observed at various

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	time points and exposures. Moreover, the biological plausibility of such observations is high, based on carcinogenesis and genotoxicity in laboratory animals. The independent panel of scientific experts noted that the data support a clastogenic mode of action for ethylene oxide, that in humans the mutagenicity includes both large-scale damage and point mutations, and that the large-scale damage may be of equal or greater importance to clastogenicity in the mode of action.
EOIC indicated that there should have been more critical discussion of the human reproductive studies conducted by Rowland et al., Hemminki et al., and Lindbolm et al.	This comment was raised previously by one of the EOIC contributors (M.J. Teta) during first-stage review of the supporting documentation. The Assessment Report acknowledges the limited weight of evidence from reproductive epidemiological studies, when considered in the context of traditional criteria for causality. It was concluded that while there are some consistent results in this regard, the available data are too limited to address other traditional criteria for causality such as strength and exposure-response, though they are supported at least to some extent, with respect to biological plausibility, by studies in animals which indicate that among non-neoplastic effects, reproductive effects occur at lowest concentration.
EOIC suggested that the estimates of ethylene oxide exposure near chemical plants should be reduced.	The Assessment Report indicates the limitations of the predicted values of levels of ethylene oxide in outdoor air in the vicinity of a production facility in Canada. Indeed, a recommendation for additional monitoring in the vicinity of point sources, as a basis for risk management, is included in the Assessment Report. EOIC has indicated that it will work with the ethylene oxide

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	production facilities to gather more information on fenceline concentration values based on actual monitoring data, as well as detailed information on any modelling data developed by the facility. While this contribution is welcomed, EOIC has submitted no additional relevant information at this time.
EOIC suggested that an additional study published in 1964 that reported no evidence of nervous system disorders in 32 occupationally-exposed males be included in the assessment report.	Inclusion of the 1964 study was raised previously by one of the EOIC contributors (M.J. Teta) during first-stage review of the supporting documentation. Though referenced in the supporting documentation, it is not included in the Assessment Report since it is not particularly germane to an assessment of risk for the general population. The text of the Assessment Report indicates that (reversible) neurological effects have been observed in some studies of individuals exposed to very high levels of ethylene oxide; however, other endpoints are considered critical for risk characterization for the general population.

References

Summary of First and Second Stage External Review on Ethylene Oxide. August 2nd, 1999. Environmental Health Directorate, Health Canada, Ottawa, Ont. www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm

ITER Peer Review Meeting Summary, August 12th, 1999. Ethylene Oxide and NDMA. Toxicology Excellence for Risk Assessment, Cincinnati, Ohio. http://www/tera/org/peer