ITER Peer Review Meeting Summary on Ethlyene Oxide & N-Nitrosodimethylamine (NMDA)

August 12, 1999
Ottawa, Ontario
Canada

An independent panel of expert scientists and risk assessors met in Ottawa to review a hazard characterization and dose-response assessment on ethylene oxide and N-Nitrosodimethylamine (NDMA). Health Canada developed both assessments as part of the Priority Substances Program under the Canadian Environmental Protection Act. This meeting was conducted by Toxicology Excellence for Risk Assessment (*TERA*), a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessments. The objective is a comprehensive overall review of the materials as provided by the combined experience of all the reviewers.

After brief introductions, the meeting began with a discussion of conflict of interest. Each reviewer certified that he or she did not have a conflict (real or apparent) with the chemicals under review or with the sponsor, or identified the potential for such conflicts. Possible conflicts were discussed with each reviewer to determine if measures were needed to manage a potential conflict (or appearance of conflict). Options included excluding the reviewer from a particular discussion and consensus, or allowing the reviewer to participate in the discussion, but not be polled for consensus. Panel members each identified themselves, summarized their backgrounds, and noted any possible conflicts. The panel agreed with the proposed plan for managing conflict of interest as documented in Attachment A, with the change to note that Dr. Walker has several manuscripts on ethylene oxide mutagenicity, rather than one, in preparation; although he is not primary author on these manuscripts.

This review meeting followed a standard *TERA* process, beginning with a close examination of the supporting documentation and important references by the panel in the several weeks prior to the meeting. At the meeting, the authors of the assessment or documentation briefly presented their work. For chemical assessment documents, the panel then systematically discussed the assessment, starting with a discussion of the qualitative weight of evidence and a determination of whether adequate data exist on which to base a risk value, followed by a discussion of the appropriate critical endpoint and studies. Next, the quantitative aspects of the assessment were discussed, including proposed cancer and non-cancer risk values, as appropriate.

Full discussion and participation were encouraged and agreement was reached by consensus. Consensus for the purpose of these meetings is defined as "an opinion held by all or most, or general agreement." The meeting was open to the public and observers from Union Carbide Corporation, Dow Chemical Canada, Inc., and U.S. EPA were present.

Assessment for Ethylene Oxide

Sponsor: Health Canada

Presenters:

- Ms. Bette Meek, Health Canada
- Dr. Robert Liteplo, Health Canada
- Dr. Michael Walker, Health Canada

Chair: Dr. Michael L. Dourson, *TERA*

Review Panel:

- Dr. Matthew S. Bogdanffy, DuPont Haskell Laboratory
- Dr. John P. Christopher, California EPA
- Dr. Michael L Dourson, Toxicology Excellence for Risk Assessment (*TERA*)
- Dr. Susan P. Felter, The Procter & Gamble Company
- Dr. Jack S. Mandel, Exponent
- *Dr. R. Julian Preston, U.S. EPA
- Ms. Ruthann Rudel, Silent Spring Institute
- Dr. Vernon E. Walker, New York State Department of Health

*Provided written comments and did not participate in discussion or consensus decisions.

PRESENTATION

Ms. Meek briefly discussed the objectives for the review and development of the assessment document. She described the Stage 1 review, which identifies potentially missing data, and the Stage 2 review, which addresses the defensibility of the hazard evaluation and exposure-responses analyses, that had already been completed and noted that this review meeting was to focus on the quality of the hazard and dose-response characterizations. The exposure assessment, risk characterization, and discussion of uncertainties, which are not the subject of this review, will be completed at a later date and included in the final documentation. Dr. Liteplo presented information on the ethylene oxide assessment. Dr. Walker answered questions regarding the modeling conducted to estimate the TC_{05}s for ethylene oxide.

The Health Canada assessment discusses the data in both humans and animals that are available for ethylene oxide. It is an irritant and has been shown to be a sensitizer, causing both anaphylaxis (Type I) and contact dermatitis (Type IV) hypersensitivity reactions. Noncancer effects include hematological changes and histopathological effects

in several organs following inhalation exposure and histopathological effects and liver damage following oral exposure. Inhalation exposure to ethylene oxide has resulted in reproductive effects in male laboratory animals and has caused fetal toxicity and developmental toxicity in both the presence and absence of maternal effects at high doses. In humans, epidemiological studies provide suggestive, but inconclusive, evidence of increased risk of spontaneous abortions. Inhalation exposure to ethylene oxide also results in neurological effects, including morphological, behavioral, and histopathological effects, in both humans and laboratory animals.

There is evidence of carcinogenicity for ethylene oxide in laboratory animals. Following inhalation exposure, leukemia, mesothelioma, and brain tumors have been observed in rats while lymphoma, uterine tumors, mammary tumors, and lung tumors have been observed in mice. Following oral exposure, forestomach tumors have been observed in rats. Several epidemiological studies investigated the cancer risk in populations exposed to ethylene oxide through the production and/or use of ethylene oxide in the synthesis of other chemicals. These studies have occasionally reported increases in mortality due to cancers of several organs, including liver, colon, breast, bladder, kidney, esophagus, stomach, brain, and pancreas. However, Health Canada found that the evidence for these cancers is neither consistent across studies nor convincing. Increased risks for lympho/hematological cancers have been reported by several studies of workers in facilities where ethylene oxide was used as a sterilizing agent; however the increases have generally been less than two-fold and not statistically significant. Sensitivity of most studies was limited by short period of follow-up. Therefore, the human studies provide suggestive, but inconclusive, evidence of increased risk for hematological cancers.

Ethylene oxide is clearly genotoxic in *in vitro* assays, causing DNA damage and gene mutations in bacteria, yeast, fungi, and mammalian cells. *In vivo* assays have also been consistently positive, providing clear evidence of somatic and germ cell genotoxicity. Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, including DNA. In humans, cytogenetic changes, including chromosome aberrations, micronuclei, or sister chromatid exchange, have been observed in the peripheral blood cells of workers exposed to ethylene oxide. While not indicators of chronic adverse health outcomes, the observation of cytogenetic effects in workers provides additional supporting evidence for the ability of ethylene oxide to interact with the genome in individuals exposed to this substance. Although the data are insufficient to support a conclusion regarding mode of action, the effects of ethylene oxide have been attributed to its ability to alkylate macromolecules. Specifically, DNA alkylation is likely to have a principal role in genotoxicity. There are no qualitative differences in ethylene oxide metabolism between animals and humans.

Cancer is considered to be the critical effect for ethylene oxide. Quantitation of the exposure-response was based on two bioassays in F344 rats (Snellings et al., 1984; Garman et al., 1985; Garman and Snellings, 1986; Lynch et al., 1984a,b) and one in B6C3F1 mice (NTP, 1987). In rats, there were dose-related increases in the incidence of splenic mononuclear leukemias, peritoneal mesotheliomas, and brain tumors. In mice, there were increased incidences of lung carcinomas, malignant lymphomas, uterine

adenocarcinomas, mammary carcinomas and adenosquamous carcinomas, and Harderian cystadenomas. Concentrations of ethylene oxide causing a 5% increase in tumor incidence over background (i.e., the Tumorigenic Concentration$_{05}$, or TC_{05}) were calculated by fitting the multistage model to the dose-response data. The TC_{05}s and the corresponding 95% lower confidence limit were adjusted for continuous exposure. The resulting TC_{05}s ranged from approximately 2 to 32 mg/m^3.

The study by Snellings et al. (1984), Garman et al. (1985), and Garman and Snellings (1986) was considered the optimal study for characterizing the dose-response because of the dose spacing, the exposure of both sexes, and the large group sizes. Final selection of a TC_{05} will be presented in the risk characterization (to be completed). To provide as much information as possible regarding the characterization of exposure-response, the SMRs for all hematological neoplasms reported by the epidemiological study of Stayner et al. (1993) were compared with the risk for the mononuclear cell leukemia in female rats (the tumors for which estimated potency was highest). In addition, the TC_{05}s were compared with the ethylene oxide concentrations associated with an increased risk of heritable mutations and with reproductive and neurological effects.

Clarifying Questions

Regarding the species differences in ethylene oxide metabolism, one reviewer asked whether it is correct that metabolism to ethylene glycol was predominant in humans and dogs, but metabolism via glutathione (GSH) was predominant in rats. Health Canada indicated that this is correct. Both pathways are considered detoxification pathways and it is the parent compound that is the putative toxin. Another reviewer asked whether the Health Canada assessment was suggesting that species with higher GSH levels were either more or less sensitive to developing tumors. Health Canada replied that the assessment document was not suggesting such a relationship. Finally, a reviewer asked if GSH levels changed as animals aged and whether this change might be the cause of the late-forming tumors observed following ethylene oxide exposure. Several panel members noted, however, that late-forming tumors were not related to GSH levels, but were common with many chemicals.

DISCUSSION

Hazard Characterization

Several reviewers noted that the document was well written and presented a large amount of data in a clear and transparent manner. Overall, the panel agreed that the conclusions made by Health Canada regarding the human, animal, and genotoxicity data were sound. Most of the panel discussion focused on the hazard characterization summary presented in Section 11.1 (pages 37-40) of the draft document.

Human Cancer Data. Health Canada concluded that the human database does not provide a convincing argument for a causal relationship between ethylene oxide exposure and cancer, but that the Stayner et al. (1993) study suggests that longer follow-up is needed to fully understand the potential for hematopoietic cancer risk. However, several panel members indicated that the characterization summary, in attempting to highlight the studies that illustrate the consistency of the data, presented the human data as more strongly positive than is warranted. For example, one reviewer noted that discussing "suggestive" findings that are not statistically significant puts too much emphasis on these data. However, another reviewer noted that nonsignificant, yet suggestive results do contribute to the overall weight of evidence. One reviewer commented that the conclusions of Stayner et al. (1993) study should be interpreted with caution because the authors' sensitivity analysis showed that their analysis was sensitive to the results of a single person in the study. However, Health Canada noted that the Stayner et al. (1993) study was considered as it contributed to the weight of evidence of causality for the entire database and because it had, by far, the best characterization of exposure. It was used for bounding of estimates from the animal studies and to demonstrate dose-response trends. It did not contribute to the quantitative assessment. Overall, the panel recommended that the paragraphs summarizing the human data be revised to better reflect the balance that is found in the body of the text.

Animal Cancer Data. Overall, the panel found that the Health Canada conclusions regarding the animal data are sound. The panel discussed the fact that the splenic mononuclear leukemia observed in the rat studies is a tumor type that is unique to the F344 strain and appears in this strain with a high background incidence. One reviewer noted that the incidence of this tumor type is highly variable, so that the effect is in part dependent on the adequate randomization of animals in the study. The cell of origin is not known, nor is it known if the tumor is even hematopoietic in origin. Also, there is no known human counterpart for this tumor. Dr Snellings, an author of the critical study who was present as an observer, confirmed that the cell of origin for these tumors could not be determined. He also noted that these tumors are late forming and were not observed before the final sacrifice. The panel recommended that the assessment document discuss this tumor type with caveats that the cell of origin is not known, it is unique to F344 rats and there is no known counterpart in humans, and that the tumor occurs with high background in F344 rats. In addition, it was suggested that the information on time-to-tumor be added to the discussion of the rationale for selection of which tumors to model in calculating the TC_{05}.

Mode of Action Data. One reviewer commented on the extensive discussion of the GST1 polymorphism. Since metabolism to ethylene glycol appears to be a more important pathway in humans than conjugation with glutathione via GST, this reviewer suggested that Health Canada reexamine the studies to determine if data are available to enhance the quantitative discussion of the importance of the ethylene glycol pathway in humans. The types of information to look for include V_{max} and Km for the metabolic enzymes and information on ethylene glycol levels in humans compared to rats. If these data are not available, then the assessment document should be revised to enhance the discussion of the lack of these data. The panel agreed with these suggestions. (NOTE: After the

meeting, Health Canada authors noted that they had checked the human studies for this type of data in preparation of the draft document and these data are not available.)

Overall, the panel agreed with the characterization of genotoxicity data presented in the document. It was recommended that the mutagenicity discussion be expanded to describe the nature of the mutagenicity caused by ethylene oxide. The panel discussed the fact that ethylene oxide is clastogenic and that the data support a clastogenic mode of action for ethylene oxide. However, one reviewer noted 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. It was also recommended that the assessment document expand the discussion of the Bastlova et al. (1993) study.

One reviewer submitted copies of two new studies (Wu et al., in press a, b) that present new methods for measuring DNA adducts and present new data on background levels of DNA adducts. These new data update the DNA adduct data presented by Walker et al. (1992) and discussed by Health Canada in the assessment document. The reviewer asked that, if possible, these new data be incorporated into the assessment.

Cancer Characterization. The final discussion of the hazard characterization section of the draft document focused on the cancer characterization presented in the last paragraph on page 40. Specifically, discussion focused on whether it is appropriate to characterize ethylene oxide as "highly likely to be carcinogenic to humans." Health Canada indicated that the characterization is based on the strength of the animal data, the data on clastogenicity in humans, the fact that the epidemiology studies are not convincingly negative, and the overall consistency of the database relative to databases for similar chemicals. Several reviewers felt that the paragraph, as written, unduly weighted the epidemiology data. The panel recommended that the paragraph be revised to decrease the emphasis on the human data and to enhance discussion of the genotoxicity and animal data as they contribute to the overall cancer characterization. No consensus was reached on recommendations for specific wording of the paragraph.

Dose Response Assessment

Overall, the panel agreed that the animal data are the appropriate basis for developing a quantitative estimate. The panel discussed the usefulness of presenting a comparison of quantitative estimates derived from both animal and human studies, as was done in the document. Several reviewers felt that such a comparison was essential to address the question of whether tumors should have been observed in humans, given the potency of ethylene oxide in animals. However, other reviewers felt that the uncertainties are too great and that too many assumptions (e.g., characterization of exposure for workers) are needed to develop quantitative estimates from the available human data to make such a comparison meaningful. The panel suggested that the human and animal comparisons be moved to an appendix. Panel members noted that there are several approaches to doing these comparisons, in addition to the one used by Health Canada. Different approaches would likely support different conclusions. Health Canada agreed, and noted that one

possibility might be to include all different comparisons in an appendix so that readers are aware of the problems associated with each one.

Critical Effect. Overall, the panel agreed that cancer is the appropriate critical effect on which to base a quantitative risk estimate for ethylene oxide. In pre-meeting comments, one reviewer noted that in situations of short-term or intermittent exposure, different dose conversions would be used, which may result in some of the noncancer effects being identified as the critical effect, rather than cancer. Health Canada noted that only continuous, long-term exposure was of concern for this assessment because its purpose was to determine if ethylene oxide met the definition of "toxic" under the Canadian Environmental Protection Act. The quantitative estimate in this assessment would not be used to set guidelines for short-term exposure. The panel recommended that a statement to this effect be added to the document.

The panel discussed heritable mutations as a potential critical effect. Health Canada noted that this effect might be of concern, but that there are too many uncertainties to confidently quantitate this endpoint. Because of this, the panel recommended removing the cumulative uncertainty of the estimate (i.e., a factor of 7, which had been estimated by the authors of the publication) from the estimation of heritable mutation risk, leaving a qualitative discussion of uncertainties only. In response to pre-meeting comments, Health Canada noted that their estimate of BMC_{05} for heritable mutations would be 1.2 mg/m^3 rather than 229 mg/m^3 if the doses are converted based on the duration of reproductive lifetime.

The panel discussed the appropriateness of doing the 5/7 days and 6/24 hour dose conversions for cancer and noncancer endpoints for ethylene oxide. Several panel members felt that Haber's Law (Response is equal to Concentration x Time) does not apply to cancer in this case and may not apply to noncancer effects. However, the panel noted that data are not available to justify eliminating the dose conversions from the quantitation. One panel member suggested that interim sacrifice data from the Snellings study might provide the data needed to study this suggestion, and another panel member offered to evaluate these data for Health Canada if they were made available.

Quantitative Estimate. Overall, the panel agreed with the estimation of TC_{05}s presented in the assessment. One reviewer noted that although the goodness of fit statistics for each TC_{05} are presented in a table, the document does not discuss them. This reviewer suggested that goodness of fit be a criterion used in weighting the TC_{05} values and selecting the final value in the ultimate Risk Characterization. The panel recommended that graphical presentation of the modeling results, as well as a discussion of the goodness of fit, be added to the document.

RECOMMENDATIONS

The panel made the following recommendations for revisions to the document:

- Overall, conclusions on the human, animal, and genotoxicity data are sound. However, the summary paragraphs should better reflect the balance in the body of the report. In particular, the summary of the human data should present a balanced evaluation of the criteria for causality rather than highlighting only the supportive data.

- The conclusions regarding mode of action are appropriate, but the discussion could be enhanced by adding quantitative information on the metabolism of ethylene oxide to ethylene glycol in humans, if available, and by enhancing the discussion of large scale damage compared to point mutations caused by ethylene oxide. The discussion of Bastlova et al. (1993) should be expanded.

- The conclusion of the cancer characterization (last paragraph on page 40) should be rewritten to decrease the emphasis on human data and to enhance the discussion of animal and genotoxicity data as they contribute to the overall cancer characterization. The panel did not reach consensus on recommended wording for this paragraph.

- A discussion of the splenic mononuclear leukemias should be added to the document. This discussion should address the fact that this tumor type is unique to F344 rats, that it occurs with a high and variable background incidence, that the cell of origin is unknown, that there is no human counterpart to this tumor, and that the tumor is late forming.

- In the quantitation of risk from heritable mutations, the quantitative uncertainty discussion (i.e., the text on the factor of 7) should be removed.

- Graphs of the modeling results for the TC_{05}s (which were inadvertently missing from the review package) should be presented with a discussion of the contribution of p-values to the goodness of fit statistics in the final document.

- Text should be added that states that the critical effect might be different for short-term exposures and that the quantitative estimate, which is based on long-term continuous exposure, may not be appropriate for short-term scenarios.

In addition, the panel made the following suggestions:

- Incorporate data on DNA adduct background levels found in papers provided at the meeting, if possible.

- With the help of a volunteer reviewer, study the data from interim sacrifices to determine if the Haber's Law dose conversions can be eliminated.

- Consider the contribution of goodness-of-fit p-values in weighting TC_{05}s for selection of a final value in the Risk Characterization.

- Move the human and animal comparisons to an appendix.

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Assessment for N-Nitrosodimethylamine (NDMA)

Sponsor: Health Canada

Presenters:

- Ms. Bette Meek, Health Canada
- Dr. Robert Liteplo, Health Canada
- Dr. Michael Walker, Health Canada

Chair: Dr. Michael Dourson, *TERA*

Review Panel:

- Dr. Matthew S. Bogdanffy, DuPont Haskell Laboratory
- Dr. John P. Christopher, California EPA
- Dr. Michael L Dourson, Toxicology Excellence for Risk Assessment (*TERA*)
- Dr. Susan P. Felter, The Procter & Gamble Company
- Dr. Jack S. Mandel, Exponent
- Ms. Ruthann Rudel, Silent Spring Institute
- Dr. Vernon E. Walker, New York State Department of Health

PRESENTATION

Ms. Meek briefly discussed the objectives for the review and development of the supporting documentation on N-nitrosodimethylamine (NDMA). She described the Stage 1 review, which identifies potentially missing data, and the Stage 2 review, which addresses the defensibility of the hazard evaluation and exposure-responses analyses, that had already been completed. She noted that this review meeting was to focus on the content of the hazard and dose-response characterizations. The exposure assessment, risk characterization, and discussion of uncertainties, all of which are not the subjects of this review will be completed at a later date and included in the final documentation. Dr. Liteplo presented information on the NDMA assessment. Dr. Walker answered questions regarding the modeling conducted to estimate the TD_{05}s for NDMA.

The Health Canada supporting document discussed that although the database for NDMA is somewhat limited, the data provide overwhelming evidence of carcinogenicity in laboratory animals. NDMA is carcinogenic in all species tested (mice, rats, hamsters), by all routes of exposure, and at relatively low doses. Tumors have been observed in a wide range of tissues including liver, Leydig cells, lungs, kidney, and nasal cavity, in the absence of significant noncancer effects, though data on the latter are limited. In addition, NDMA is carcinogenic in laboratory animals after single exposures and following

repeated exposure for short periods. In humans, there is suggestive evidence of an association between exposure to NDMA and gastric and lung cancers. Noncancer effects include liver, brain, lung, kidney, and spleen damage. In addition, studies in animals suggest that NDMA is embryotoxic and may cause suppression of cellular and humoral immune responses.

NDMA is mutagenic and clastogenic in both *in vitro* and *in vivo* assays. Genotoxic effects have been observed in tissues (i.e., liver, kidney, and lung) where tumors occur following exposure to NDMA. NDMA is metabolized to the methyldiazonium ion which forms DNA adducts, in particular O^6-methylguanine, which is likely to make a significant contribution to the carcinogenicity of NDMA.

A study reported by Brantom (1983) and Peto et al. (1991a,b) was selected as the basis for the quantitative estimate. In this study, NDMA was administered in drinking water to 15 dose groups of Colworth-Wistar rats (60/sex/group). Doses of NDMA causing a 5% increase in tumor incidence over background (i.e., the Tumorigenic Doses, or TD_{05}s) were calculated by fitting the multistage model to the dose-response data. Because the large number of dose groups resulted in a poor fit of the model, two additional approaches were used. First, quadratic models were fit to the full set of data; second, the number of dose groups was reduced by dropping the upper doses and collapsing adjacent similar dose groups together. The TD_{05}s ranged from approximately 0.034 to 0.078 mg/kg/day.

Clarifying Questions

One reviewer asked if a time-to-tumor-analysis was used in the modeling of carcinogenic potency. Health Canada responded that the data needed to conduct such an analysis were not available; therefore, the document presented the information from the analysis conducted by Peto et al. (1991a,b).

DISCUSSION

Hazard Characterization

Animal Data. Overall, the panel agreed with Health Canada's characterization of animal data, and the panel agreed that cancer is the primary effect of concern for NDMA. The panel discussed the reproductive/developmental study by Anderson et al. (1978) in which fetal toxicity was observed in mice at a dose of 0.02 mg/kg-day, which is lower than the doses at which tumors were observed. Health Canada noted that this study was limited to a single dose and that there were no effects other than an increase in the number of stillborn pups. Also, Health Canada noted that the authors' concluded that their results were preliminary. The panel recommended that the Anderson et al. (1978) study be described in more detail, including a discussion of its limitations. Also, one reviewer suggested that the first sentence of the last paragraph that in Section 11.2.2 be revised to

indicate that with the exception of Anderson et al. (1978) non-neoplastic effects of NDMA were observed at doses greater than those which caused increases in tumor incidence. This reviewer also suggested that the section state that the issue of reproductive/developmental toxicity needs additional study.

Mode of Action. Overall, the panel agreed with the characterization of mode of action. One reviewer noted that NDMA is a chemical for which the mode of action is clearly known and that the document presents the mechanism information very well. However, the two reviewers made some suggestions for revision to enhance the mode of action discussion. One reviewer suggested that the metabolism section could be enhanced by separating out the discussion of DNA adducts, the role of O^6-methylguanine transferase in species and age differences in adduct content, and the relationship to carcinogenic responses and shapes of the dose-response curves. This reviewer noted that the rate of metabolism of NDMA appears to be similar in humans and animals, but the rate of repair of DNA adducts via O^6-methylguanine transferase appears greater in humans than rodents. In addition, this reviewer noted that formaldehyde is a metabolite of NDMA and suggested that the document should discuss the possible role of formaldehyde in NDMA carcinogenicity. Another reviewer suggested that, if available, the document should include evidence of the formation of other pro-mutagenic DNA adducts other than O^6-methylguanine. Such evidence would include the increased frequency of G:C to A:T transitions at CpG sites and the increased frequency of A:T to T:A transversions.

Dose Response

The panel agreed with the critical study (Brantom, 1983; Peto et al., 1991a,b) and data set, and further agreed that the choice of dose-response analysis was appropriate. The resulting TD_{05}s ranged from 0.034 to 0.082 mg/kg/day.

RECOMMENDATIONS AND SUGGESTIONS

- The panel recommended that the Anderson et al. (1978) study be described in more detail, including a discussion of its limitations.

- Two reviewers suggested revisions to enhance the mode of action discussion including addressing species differences in DNA adduct repair, the role of metabolites in the carcinogenic response, and the formation of other pro-mutagenic DNA adducts.

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Appendix A
Managing Potential Conflicts of Interest
ITER Peer Review Meeting
August 12, 1999
(Accepted by panel)

ITER peer reviewers donate their time and talents to this effort. They are selected based upon their expertise and qualifications and are employed by many types of organizations. *TERA* strives to create a balance of expertise and affiliations for each meeting. However, individual peer reviewers are representing their own expertise and views, not those of their employer. The *TERA* Board of Trustees approves *ITER* peer reviewers for inclusion in this program. A complete list of approved reviewers and more information on the *ITER* peer review program are available at http://www/tera/org/peer. Additional, *ad hoc* reviewers are selected to participate for their special expertise that may be needed for a particular chemical or discussion.

TERA requested that each peer reviewer identify potential conflicts of interest related to the review of the health risk assessment of ethylene oxide and N-nitrosodimethylamine, and/or the sponsor of these assessments, Health Canada. Each reviewer has signed a statement indicating that he or she does not have a conflict of interest concerning this assessment.

The following statements were considered by the panel and agreed upon at the meeting.

Matthew Bogdanffy – Dr. Bogdanffy is the Director of Biochemical Toxicology at the DuPont Haskell Laboratory. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

John Christopher - Dr. Christopher is a Toxicologist with the Department of Toxic Substances Control of the California Environmental Protection Agency (Cal EPA). Cal

EPA regulates various aspects of production, use, sale or disposal of many chemicals, including those under discussion. However, Dr. Christopher does not have a specific conflict of interest with these chemicals and will participate fully in the discussion and consensus. Dr. Christopher requested inclusion of the following note: "Dr. John Christopher performs scientific peer review for *TERA* as a private individual. His employer, the California Department of Toxic Substances Control, is not bound in any way by the opinions he expresses or by consensus agreements to which he chooses to be a party."

Michael Dourson – Dr. Dourson is the Director of Toxicology Excellence for Risk Assessment (*TERA*). Dr. Dourson will serve as panel chair. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

Susan Felter – Dr. Felter is a Toxicologist with The Procter & Gamble Company. She has no conflicts and will participate fully in all discussions and polling for consensus**.**

Jack Mandel – Dr. Mandel is an epidemiologist with Exponent. He no conflicts and should participate fully in all discussions and polling for consensus**.**

R. Julian Preston – Dr. Preston is Director of the Environmental Carcinogenesis Division of the U.S. Environmental Protection Agency. Dr. Preston was asked to be an *ad hoc* reviewer because of his experience evaluating the genetic toxicity of ethylene oxide. Dr. Preston has received funding in the past by the Ethylene Oxide Industry Council to conduct research and write a journal review on ethylene oxide effects. The content of both was entirely initiated by Dr. Preston. He does not feel that this is a conflict for the present review. Dr. Preston is unable to attend the meeting and has provided written comments on ethylene oxide for the panel's consideration, but he will not participate in reaching consensus.

Ruthann Rudel – Ms. Rudel is a Senior Scientist with the Silent Spring Institute. She has no conflicts and will participate fully in all discussions and polling for consensus**.**

Vernon Walker -- Dr. Walker is a Research Scientist with the Wadsworth Center of the New York State Department of Health. Dr. Walker provided comments to Health Canada in the Stage 1 External Review of ethylene oxide. He is currently finishing several manuscripts concerning the mutagenicity of ethylene oxide on research on DNA alkylation and mutagenicity for ethylene, which was performed from 1994 to 1997 at the University of North Carolina (with Jim Swenberg); however, his role in completing the manuscripts is peripheral. Ethylene oxide was used as a positive control to understand ethylene. The Chemical Manufacturers' Association supported this work at UNC, but Dr. Walker is not currently receiving any funding. Dr. Walker will be involved in future research at the Wadsworth Laboratory on butadiene (ethylene oxide will be used as a positive control), which will be funded by the Health Effects Institute. Dr. Walker and *TERA* do not think that this work constitutes a conflict of interest and recommend that Dr. Walker participate fully in all discussions and polling for consensus. The panel agreed that Dr. Walker will participate fully in all discussions and polling for consensus.