ITER Peer Review on Ethylene Glycol and Dimethylformamide Meeting Summary Report

An independent panel of expert scientists and risk assessors met in Ottawa on February 14, 2000 to review hazard characterization and dose-response assessments on ethylene glycol and dimethylformamide. A subsequent conference call was held on March 29, 2000 to discuss remaining questions on ethylene glycol. Health Canada developed both assessments as part of the Priority Substances Program under the Canadian Environmental Protection Act. This meeting and conference call were 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 and conference call 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. The panel agreed with the proposed plan for managing conflict of interest as documented in Attachment A.

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 assessments briefly presented their work. 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 risk values.

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 and conference call were open to the public and observers from Union Carbide Corporation, Dow Chemical Company, and PPG Industries (U.S. and Canada) were present at the meeting and observers from the Chemical Manufacturers Association (CMA) and Union Carbide Corporation were present on the conference call.

Assessment for Ethylene Glycol

Sponsor: Health Canada

Presenters: Ms. Bette Meek, Health Canada

- Dr. Robert Liteplo, Health Canada
- Dr. Michael Walker, Health Canada

Chair: Dr. Kenneth Poirier, *TERA*

Review Panel:

- Dr. Mohamed S. Abdel-Rahman, New Jersey Medical School, Department of Pharmacology and Physiology
- *Dr. Charles O. Abernathy, U.S. Environmental Protection Agency, Office of Water
- Dr. John P. Christopher, California Environmental Protection Agency, Department of Toxic Substances Control
- Dr. James J. Collins, Solutia, Inc.
- Dr. Joan T. Colman, Syracuse Research Corporation
- *Dr. Moiz M. Mumtaz, Agency for Toxic Substances and Disease Registry
- Dr. Kenneth A. Poirier, Toxicology Excellence for Risk Assessment (*TERA*)
- Mr. John E. Whalan III, U.S. Environmental Protection Agency, Office of Pesticide Programs

* Were not able to attend the conference call on March 29, 2000.

The review of Health Canada's ethylene glycol assessment took place in a meeting (February 14, 2000) and a subsequent conference call (March 29, 2000). At the conclusion of the meeting, Health Canada had unanswered questions regarding the pathology findings of the DePass et al. (1986) study. They contacted Dr. Robert Maronpot, one of the authors of the DePass et al. (1986) study and currently with NIEHS, to help interpret the results of the study. As a result, Health Canada revised the dose-response analysis and calculation of the Tolerable Intake (TI). A conference call was held with the peer review panel on March 29, 2000 to discuss the revised TI. The panel and other participants were provided with Health Canada's revised dose-response documentation and the text of several emails between Dr. Maronpot and Ms. Meek. Six of the original peer review panel were able to attend (Mohamed Abdel-Rahman, John Christopher, James Collins, Joan Colman, Kenneth Poirier and John Whalan III). In addition, *TERA* asked Dr. Edward Ohanian of the U.S. EPA to provide the panel with his opinion on the histopathology of the two key studies and participate as a resource for the peer review panel (not as a peer reviewer) at the March 29 conference call. Dr. Robert Maronpot also attended to answer questions regarding the study and kidney pathology. The teleconference was open to the public and observers from Union Carbide and the Chemical Manufacturers Association listened.

The summary of the presentation and discussion below presents the final recommendations of the meeting and conference call.

PRESENTATION

Dr. Robert Liteplo and Ms. Bette Meek briefly summarized the Health Canada assessment on ethylene glycol. Dr. Liteplo noted that the toxicological effects of ethylene glycol are primarily due to actions of metabolites, and based on the available data there are no apparent qualitative differences in metabolism between humans and laboratory animals. Renal damage (crystal formation) has been observed in humans acutely poisoned and also in laboratory animals in a number of short- and long-term exposure studies. Male rats are the most sensitive sex and species. Kidney damage has been linked to deposition of calcium oxalate crystals in the kidney. Developmental effects, including malformations, have been observed in both rats and mice at exposures equal to or somewhat less than those inducing maternal toxicity, but greater than doses associated with kidney damage. It has been suggested that developmental effects may be due to a combination of metabolic acidosis and/or direct toxicity induced by glycolic acid. However, an additional role of other metabolites has not been fully excluded at this time.

Health Canada selected the data from an unpublished study by Gaunt et al. (1974) to be the optimal data set for derivation of a benchmark dose and Tolerable Intake (TI). The Gaunt study was preferred over other studies (e.g., DePass et al., 1986) because: it included four dose levels with the two highest showing significant increases in tubular damage; there were more doses in the lower dose range near some putative no effect level; dose spacing was 2- to 3-fold, compared to the 5-fold in the DePass et al. (1986) chronic study; and, the study reported incidences of individual lesions and total animals with tubular damage. However, the group sizes were relatively small (n=15) and exposure was for 16 weeks.

Health Canada considered the chronic dietary study by DePass et al. (1986) in rats and mice inadequate for a meaningful analysis of exposure-response. Although there were larger numbers of animals per group there were only three dose levels and after 18 months on study, all male rats in the high-dose group (1000 mg/kg bw/day) had died or were sacrificed when they became moribund. Effects were only observed at the top dose. Health Canada was able to obtain additional data on the six- and twelve-month interim sacrifices from the study sponsor, Union Carbide, which indicated that there appears to be some incomplete reporting of incidence of several early renal lesions in the published account of the study. For example, the incidence of calcium oxalate crystalluria at the high dose was 6/10 at 6 months and 10/10 at 12 months, while DePass reported overall incidence for this endpoint of 16/116. The 16/116 appears to be a simple sum of the interim sacrifice incidence over a denominator of total animals in the study. Other renal lesion incidence data appeared to be reported in a similar fashion in the DePass publication. It was not clear how data in DePass were derived or perhaps some endpoints were examined at early stages and others at late stages. Health Canada felt that these uncertainties precluded use of this study for exposure response of renal effects in male rats. Additional consultation with one of the study pathologists confirmed the inadequacy of histopathological reporting in the bioassay.

Based upon results presented in Gaunt et al. (1974), a benchmark dose (BMD) at the 5% response level was selected based on the total incidence of animals with tubular damage. The BMD_{05} was 49 mg/kg bw/day, with the 95% lower confidence limit on this BMD_{05}

equal to 22 mg/kg bw/day. Health Canada proposed dividing the BMD_{05} by an uncertainty factor of 1000 (10 for interspecies variation, 10 for intraspecies variation and 10 for subchronic-to-chronic extrapolation) resulting in a TI of 0.05 mg/kg bw/day for ethylene glycol. In support of the uncertainty factor, Health Canada noted that the proportions of oxalate excreted by humans and rats indicates that humans may be more sensitive to acute effects than rodents. Some limited data suggest that the specific activity of alcohol dehydrogenase (the first enzyme in the metabolism of ethylene glycol) is somewhat higher in human liver extracts than in rodents. With further information on the DePass et al. (1986) study, Health Canada determined that the uncertainty factor of 10 to account for the less than chronic duration of the critical study was needed. Health Canada also concluded that the TI based on renal damage in male rats would be protective for potential developmental effects in mice.

Data from laboratory studies with human volunteers, and on tissue-specific toxicity in animals were considered inadequate for meaningful analysis of exposure-response via inhalation. Data were also inadequate for a dose-response analysis for dermal exposure. The TI based on renal damage from dietary exposure is likely to be protective for effects of ethylene glycol administered dermally.

Ms. Bette Meek briefly discussed the objectives for the review meeting and their process for development of the assessment documents. She emphasized that the review meeting is one step in a multi-step process for completion and approval of the assessment. The advice from this panel will be considered in finalizing the supporting document and Assessment Report. After this meeting, Health Canada will revise the text, add the exposure information and reach a conclusion regarding toxicity under the Canadian Environmental Protection Act. Prior stages of review included First Stage Review where Health Canada circulated the draft supporting document to researchers and experts in stakeholder groups to address adequacy of coverage and accuracy of presentation. The comments from that stage are used to assimilate critically the data in terms of their implications for hazard characterization and exposure-response analysis. The Chemical Manufacturers Association (CMA) in the United States provided comments from its Ethylene Glycol panel during the First Stage Review. Health Canada distributed to the panel documentation, which summarized the nature of the comments received and Health Canada's response to the comments. Ms. Meek noted that the comments from CMA addressed issues beyond what was requested (i.e., adequacy of coverage and accuracy of presentation of the toxicological data).

After the February 14 peer review meeting, Health Canada consulted with Dr. Robert Maronpot who was one of the pathologists for the DePass et al. (1986) study, to clarify what lesions were present and at what doses in that study. The panel considered Dr. Maronpot's written comments for the conference call on March 29, 2000.

In his remarks at the beginning of the conference call, Dr. Maronpot elaborated on his written comments and noted that the DePass study took place over 20 years ago and it is difficult for any of those involved to remember all the details of what was done and why. He indicated that it is possible that two different pathologists read the slides; he may have

read those from the earlier sacrifices and Dr. Garman the later. Because of the problems with nomenclature, he strongly recommended that the slides be reread by a single pathologist who would use today's standard practices of assigning severity ratings and look for the dose where the incidence in lesions cuts off. Regarding the presentation of the data in the published report, Dr. Maronpot noted that it appears that a conscious decision was made by the lead author/s to collapse the data for journal presentation. In addition, the focus of the study was likely on cancer and not the non-neoplastic lesions of interest to this assessment.

Dr. Maronpot noted that regarding the biology of the renal lesions, two concurrent lesions were being seen in this study - spontaneous nephropathy and oxalate nephrosis. There is a high incidence of spontaneous nephropathy in rats, with greater incidence in males than females. In addition, there is a constellation or series of changes that worsen with age. Tubular hyperplasia may be seen early on and by two years almost every part of the nephron and all nephrons are affected. Many xenobiotic agents exacerbate this spontaneous nephropothy with severity much greater in the treated animals than the controls. Oxalate nephrosis was occurring simultaneously with the spontaneous nephropathy, creating a complex situation. He believes that the term oxalate nephrosis was used to indicate that this was a separate treatment related effect, separate from the nephropathy.

Dr. Maronpot thought that if the slides were reread, that there is likely to be enhanced spontaneous nephropathy seen, based on the severity originally reported. He reiterated that he believes that if the Gaunt et al. (1974) study had continued, the lesions seen at 16 weeks would have progressed in severity and incidence.

Dr. Edward Ohanian of the U.S. EPA was asked by *TERA* to participate in the conference call as an additional resource to the panel on interpreting the histopathology of the two key studies, and to provide his opinion on the use of these two studies as the basis for a tolerable intake. His bottom-line conclusion was that the presentation of renal lesions in the DePass et al. (1986) study is inadequate to determine treatment-related progression of nephropathy. He noted a number of reasons.

- Throughout the performance of this study there was a lack of severity grading based on microscopic renal tubular and parenchymal changes. These changes would range from slight to marked and would differentiate the extent and progression (including severity) of oxalate-related lesions between control and treated animals.

- The introduction of a general pathological category such as "glomerulonephrosis" at the 18 and 24- month evaluation is quite an unusual practice in pathological examination. Glomerulonephrosis is accompanied by a number of individual nephrotoxic manifestations ranging from tubular hyperplasia to protein casts. A consistent grading scheme, terminology and diagnostic criteria are crucial to evaluate the onset and progression of treatment and or age-related morphological changes leading to a cascade of events associated with oxalate nephrosis.

- The reporting of lesions as the sum of numbers of animals with lesions at interim sacrifice over the total number of animals on test is quite unusual. The statement on page 552 of the DePass et al. (1986) publication "for ease of presentation, the data are not listed by time of appearance of the lesion" does not quite address the problem nor justify this practice.

Dr. Ohanian recommended that the DePass study slides be reread using a modern severity grading scheme to resolve the questions raised by the published study. He also expressed the opinion that were the Gaunt study to have continued, then one would expect to see a progression in kidney lesions in the treated rats.

DISCUSSION

Hazard Characterization

Several reviewers noted that the document was well written and the data were presented well. No additional data were identified by the peer review panel for inclusion in the assessment. Most of the discussion focused on selection of the critical study and endpoint for calculation of the benchmark dose. Panel members discussed the usability of the data from the DePass et al. (1986) study for this assessment. They also discussed the histopathology findings of that study and the information provided by Drs. Maronpot and Ohanian.

Health Canada outlined their concerns with the DePass study. The initial primary reason for their not using the DePass study for derivation of the TI was that it does not include adequate data on dose-response and that the dose-response curve is so steep. Health Canada scientists pointed out the uncertainty about the real incidence of the early lesions at the 200 mg/kg bw/day level, because they are not as reported in the published paper. They were also concerned about the tubular hyperplasia interim sacrifice data (which indicated that the incidence of this lesion was increased at six months, but was lower at 12 months).

A reviewer commented that the lesions seen at the various time periods in the DePass study appeared consistent with a progression of renal lesions over time. Thus, the mild lesions seen early in the study may not be seen later on because the more severe damage at later time periods precluded their occurrence and/or detection. Dr. Maronpot reinforced this possibility in his comments. An issue is what denominator is appropriate for incidences of lesions seen only at the interim sacrifices.

A reviewer disagreed with the suggestion that the 200 mg/kg bw/day from the DePass study may be a No Observed Adverse Effect Level (NOAEL), noting that the next higher dose is a Frank Effect Level (FEL), not just a toxic endpoint. This reviewer did not think it appropriate to use a FEL for the basis of the TI.

A reviewer noted that use of different strains of rats, as well as the usual variability in any population might explain some of the differences in response in the two studies. Dr.

Maronpot was asked about a statement in his written comments regarding the possible influence of the strain of rat and the diet used on the outcome of these studies. Dr. Maronpot indicated that it is widely accepted dogma that strain, diet and sex of animals influences incidence of spontaneous nephropathy. The predilection for renal lesions is more severe in rats than mice, in males more than females, and in Sprague Dawley and Wistar rats than in Fischer rats. In addition, one of the biggest factors in occurrence of spontaneous nephropathy is the amount of protein in the diet. The Gaunt study used a more sensitive strain (Wistar) than DePass (Fischer), which may account for some of the difference seen. Those present were not familiar with the diet used in the Gaunt et al. (1974) study (Spratts Laboratory No. 1 diet) so it was unclear whether the respective diets would have contributed to the differences in results.

Dr. Maronpot was also asked about his expectation of a steep dose-response curve. Dr. Maronpot stated that it is his general feeling, given the reproductive, teratology and pathological studies he has done for ethylene glycol, that while it may not be a steep dose-response curve *per se*, there appears to be a "precipitous" point, below which one does not see lesions, but above which most or all of the animals show changes.

A reviewer noted that while the DePass study does not provide dose-response information and the "curve" is steep, uncertainty is also associated with the Gaunt study, particularly with the small number of animals used (15 per dose group).

The panel reached consensus that the Gaunt et al. (1974) study is the most appropriate study and that it provides the best data upon which to derive the TI. Upon the panel's recommendation, Health Canada revised their text to more explicitly describe why the Gaunt study, rather than the DePass study, was preferred for the assessment.

Several reviewers noted that it would be helpful to have the DePass study slides reread to resolve the questions raised during the development of this assessment and its review. In response, Ms. Meek noted that the Gaunt study was more sensitive in that it used a more sensitive strain of rat and questioned how one would use information from DePass to inform the assessment. She also indicated that they are under a time constraint to finish fairly soon but will be delineating all the uncertainties in the Assessment Report.

The panel also discussed the developmental and reproductive data. One reviewer asked why a BMD was not presented for the developmental results from Neeper-Bradley et al. (1995) as part of the analysis to select the critical effect. Health Canada responded that this study did not provide the litter specific data, which, are necessary for a benchmark dose analysis, and therefore, Health Canada used the no effect levels. Health Canada indicated that they had calculated BMDs for the data available (occurrence in litter /total litters examined and occurrence in fetus /total fetuses examined) but had not included this information in the document. The panel recommended that the document include a description of these BMDs for crude comparison purposes to assure the reader that a BMD for this endpoint would not be lower than that for the kidney effects.

One reviewer pointed out that the key oral studies for developmental/reproductive effects administered ethylene glycol by different methods, which may contribute to where the no effect level is seen. For example, administration of ethylene glycol in drinking water (Lamb et al., 1985) resulted in a higher no effect level than administration by gavage (Neeper-Bradley et al., 1995). The panel suggested that the document highlight in the hazard characterization section the potential effect of mode of administration on peak blood levels.

The panel discussed the toxicokinetic and metabolism information and the mode of action section the document. Reviewers stated that the mode of action discussion was easy to read and well documented, and that the conclusions were sound. Reviewers made several editorial suggestions:

- include any human data to show how humans are different from rats (particularly with regard to alcohol dehydrogenase and the potential for humans to be more sensitive);
- include information on progression of nephropathy over time; and,
- clarify the comparison of minimum human lethal dose to animal LD_{50}s in the discussion of relative sensitivity.

It was also suggested that the immunohistochemical study cited in the mode of action section might be more appropriately discussed in the animal effects discussion as it provides support for inclusion of interstitial nephritis. One reviewer suggested that the statement "humans appear to be more sensitive" should be softened as the animal and human data are not comparable, and the human data are based on case reports in humans, in which dose levels are very difficult to estimate.

A reviewer asked for any data specifically related to alcoholics exposed to high doses of ethylene glycol. Health Canada indicated they did not find data of this type. However, an observer, Dr. Carney of Dow Chemical, noted that downstream glycolic acid oxidase is a rate-limiting enzyme. The potency of aldehyde dehydrogenase for ethanol is higher compared to the ethylene glycol; therefore, ethanol is used to detoxify ethylene glycol exposure by inhibiting metabolism cascade.

Exposure-Response Analysis

The panel discussed which kidney lesion(s) would be most appropriate for the quantitative risk estimate. Health Canada had consulted with Dr. Douglas Wolf, a pathologist from the U.S. EPA, who recommended that the total incidence of tubular damage was most appropriate rather than calculating benchmark doses on a particular lesion. After discussing the various lesions and progression of lesions, the panel agreed with basing the quantitative estimate on total tubular damage. They discussed that although the mode of action focuses on oxalic acid, one cannot preclude the role of other metabolites in renal toxicity. The panel suggested adding a qualifying statement regarding this in the document.

A reviewer asked why Health Canada did not select the lower limit of the BMD_{05} and why they selected the 5% level, rather than 10%. Health Canada responded that there is no set standard for use of the BMD or its lower limit, but in general people are not comfortable with a wide spread between the lower confidence limit of the BMD_{05} and the BMD_{05} itself, particularly when the lower confidence limit falls considerably lower than what one thinks the biological data indicate the NOAEL might lie. They also stated that their initial practice had been to use the 5% response level for cancer and they continue to use 5% for non-cancer as well.

The panel reached consensus that the 16-week incidence data from the Gaunt et al. (1974) study, combining the incidences of total tubular damage is the most appropriate data for calculation of the BMD.

The panel discussed the selection of uncertainty factors. Reviewers did not disagree with the two 10-fold factors for inter- and intra-species variability but recommended clarifying the text on relative sensitivity of humans and laboratory animals. In discussion of the 10-fold factor incorporated for subchronic-to-chronic extrapolation most panel members felt that a 10-fold factor was too high, but they could not find an acceptable justification for using less than 10-fold default value. One reviewer suggested that the Gaunt study at 16 weeks should be considered chronic since it is greater than the usual 90-days. The other reviewers and Health Canada disagreed and said that although it is slightly longer than the usual 90-day subchronic study, it should not be considered chronic, particularly because there is evidence that the lesions seen in 16 weeks would increase in severity and incidence if treatment had continued and the animals had aged. The panel reached consensus that the 10-fold factor for subchronic-to-chronic uncertainty proposed by Health Canada was appropriate. The panel agreed with a tolerable intake of 0.05 mg/kg bw/day (49 mg/kg bw/day divided by 1000) for ethylene glycol.

At the February 14 meeting, the panel questioned a statement regarding rapid elimination of the compound and noted that bioaccumulation is not part of the mode of action. Rather, toxicity arises from elimination of oxalate. The panel suggested removing the statement on rapid elimination. (Health Canada agreed and revised this discussion prior to the conference call).

The panel briefly discussed inhalation and dermal routes of exposure. They agreed with Health Canada that the data are generally inadequate to develop risk values for either route. However, if an inhalation Tolerable Concentration were needed, the panel recommended that it would be more appropriate to use the nose-only inhalation study by Tyl et al. (1995) rather than the whole body study. In the whole body study too much of the oral and dermal exposure cannot be separated from the inhalation exposure.

RECOMMENDATIONS

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

- The explanation for using the Gaunt et al. (1974) study, rather than DePass et al. (1974), should be made more explicit in the documentation.

- Include a description of the BMDs from the developmental study of Neeper-Bradley et al. (1995) for crude comparison purposes. This will assure the reader that a BMD for this endpoint would not be lower than for kidney effects.

- Clarify that the text in the uncertainty factor section on relative sensitivity of humans and laboratory animals is provided as justification for not attempting to use a data-derived factor for cross-species extrapolation.

- The panel agreed with Health Canada, that the data are generally inadequate to develop risk values for either the inhalation or dermal routes, however, if an inhalation Tolerable Concentration were needed, the panel recommended that it would be more appropriate to use the nose-only inhalation study by Tyl et al. (1995).

In addition, the panel made the following suggestions:

- Add a qualifying statement that the role of other metabolites in renal toxicity cannot be precluded.

- Highlight information regarding mode of administration differences in the key studies in one discussion.

REFERENCES

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Assessment for N,N-Dimethylformamide

Sponsor: Health Canada

Presenters: Ms. Bette Meek, Health Canada

- Mr. George Long, Health Canada
- Dr. Michael Walker, Health Canada

Chair: Dr. Kenneth Poirier, *TERA*

Review Panel:

- Dr. Mohamed S. Abdel-Rahman, New Jersey Medical School, Department of Pharmacology and Physiology
- Dr. Charles O. Abernathy, U.S. Environmental Protection Agency, Office of Water
- Dr. John P. Christopher, California Environmental Protection Agency, Department of Toxic Substances Control
- Dr. James J. Collins, Solutia, Inc.
- Dr. Joan T. Colman, Syracuse Research Corporation
- Dr. Moiz M. Mumtaz, Agency for Toxic Substances and Disease Registry
- Dr. Kenneth A. Poirier, Toxicology Excellence for Risk Assessment (*TERA*)
- Mr. John E. Whalan III, U.S. Environmental Protection Agency, Office of Pesticide Programs

PRESENTATION

Mr. George Long briefly presented the data on N, N-Dimethylformamide (DMF), and the conclusions of the Health Canada document. He noted that DMF is a universal organic solvent with a very low rate of evaporation; its primary use in Canada is as a carrier solution for pesticides. Most releases are to the air and therefore, inhalation is the exposure focus. Human data from case reports and cross-sectional studies indicate the liver is the target organ, with reports of adverse clinical symptoms, increases in serum hepatic enzymes, and histological effects on the liver. There is no consistent evidence of increases in tumors in humans, although the data are extremely limited, and the database on genotoxicity is inconclusive.

The liver is also the target organ in laboratory animal studies with increased liver weights, serum hepatic enzymes, and histological effects seen. Mice are more sensitive than rats. No increases have been seen in tumor incidences in animal studies, and genotoxicity studies are negative. Some reports of reproductive effects have been seen at doses higher than those causing effects in the liver, and some developmental effects have been seen, but only at maternally toxic doses.

The human studies are limited, but they are consistent across the database, with no effects on the liver seen at exposures up to 6 ppm. Cirla et al. (1984) and Fiorito et al. (1997) are key studies in which workers were exposed to mean concentrations of 7 ppm, and increases were seen in serum hepatic enzymes. A Tolerable Concentration (TC) for inhalation exposure was derived using 7 ppm as the LOAEL (Lowest Observed Adverse Effect Level) for increases in serum hepatic enzymes in humans, 8 hours/24 hours and 5 days/7 days to convert from intermittent to continuous exposure, and an uncertainty factor of 50 [10 for interindividual variation and 5 to address use of LOAEL rather than NOAEL (No Observed Adverse Effect Level) and less than lifetime exposure]. The TC is 0.03 ppm or 0.1 mg/cu.m. [Note: Incorrect values in original meeting summary. These were corrected on February 20, 2001.] Though not strictly comparable, since they were based on different types of hepatic effects, benchmark concentration modeling on laboratory animal data resulted in BMCs that were higher than comparable values seen in human studies.

DISCUSSION

Hazard Characterization

Several reviewers noted that this document was also well written and thorough. The panel agreed that the conclusions made by Health Canada regarding the data were sound. The review panel agreed that liver toxicity is clearly the critical effect with evidence from case reports, studies in occupationally exposed humans, and studies in laboratory animals. They agreed that the available data were adequate upon which to derive a risk estimate.

The panel agreed that the appropriate data were considered for kinetics and metabolism and the conclusions were sound. One reviewer noted formation of formaldehyde in the liver might contribute to toxicity. Another reviewer noted that formaldehyde and formic acid (metabolites of DMF) could affect the optic nerve. A third reviewer observed that the human studies were all in men (with the exception of a metabolism study of 5 men and 5 women). The panel suggested that Health Canada might mention these last two items in their document.

The panel discussed the observation of the effect of alcohol consumption with DMF exposure. The limited data available on this were presented in the document, but the data are not adequate to explain clearly what is happening. Panel members suggested that Health Canada might include a discussion about the competition for aldehyde dehydrogenase by alcohol and DMF.

The panel discussed the available human data. One reviewer highlighted some of the limitations of these studies (which are common to many occupational studies):

- whether the exposure levels are what the workers actually received as current exposures are generally lower than historic which would lead to underestimating exposure (this is relevant when effects are considered to be a result of exposure over time),
- variability in the actual exposures received by the individual workers, and
- whether average exposure is the correct metric to use.

The reviewer noted that age might be a confounding factor. While these study populations are relatively old, age had not been controlled for completely. Alcohol consumption is very important with DMF and was controlled for partially, but some workers in these studies stopped drinking because of alcohol intolerance. Exposure to other liver toxins such as toluene, ketones and alcohol may confound the results. Health Canada indicated that this type of information would be included in the uncertainty discussion of the final document.

The panel agreed with the rationale presented for selection of critical studies.

Exposure-Response Analysis

The panel discussed the adversity of the effect of elevation of liver enzymes and noted that these are small increases being seen in these studies. Reviewers agreed that the 2-fold increase in enzyme levels is a mild response, that it is probably sub-clinical, a biological effect which precedes a pathological effect, and that with continuous exposure the pathological effect will follow. They discussed whether this should be labeled a NOAEL, LOEL (Lowest Observed Effect Level) or LOAEL. The panel agreed with the designation of the effect level as a LOAEL and that consideration of the minimal adversity of the effect should be considered in the selection of uncertainty factors. They recommended that if the effect is labeled a LOAEL, then it is most appropriately qualified as minimally adverse and this should be considered in the selection of uncertainty factors. The panel agreed with use of the time weighted average or mean concentration of 7 ppm from the Cirla et al. (1984) and Fiorito et al. (1997) studies, respectively, as the basis for the Tolerable Concentration. They recommended that Health Canada explicitly discuss the minimal nature of the effect at the 7 ppm concentration.

Health Canada used a duration adjustment of 8 hours/24 hours and 5 days/7 days to convert the occupational exposure to a continuous exposure concentration. The panel noted that they could also have adjusted the occupational exposure by daily respiratory volume (10 cu. m./day for occupational exposure during an 8-hour work day divided by 20 cu. m./day for the default human 24-hour volume), which is another common approach. This would impact the resulting TC slightly. Health Canada indicated that they used 8/24 to be consistent with other assessments conducted in the CEPA program; however, they may consider the other approach in revising their methods upon completion of this phase of the Priority Substances program.

Health Canada proposed an uncertainty factor of 50 (10 for intraspecies variability and 5 for use of a minimally adverse effect and less than lifetime exposure). The panel recommended that the uncertainty factor discussion more clearly explain that the factor of five is primarily for consideration of the less than lifetime exposure in the principal study and that the effect seen at 7 ppm is considered minimally adverse.

RECOMMENDATINS AND SUGGESTIONS

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

- Include more explicit discussion to define the "minimally" adverse nature of the LOAEL.

- In the uncertainty factor discussion, more clearly explain that the factor of five is primarily for consideration of the less than lifetime exposure in the principal study, and that the LOAEL of 7 ppm is minimally adverse.

In addition, the panel made the following suggestions:

- Include an additional statement on the increased sensitivity to DMF upon co-exposure to alcohol is likely a function of the competition for aldehyde dehydrogenase between ethanol and DMF.

- Note that all the critical studies appear to have studied only men.

- Consider noting that formaldehyde and formic acid (metabolites of DMF) could effect the optic nerve.

REFERENCES

Cirla, A.M., G. Pisati, E. Invernizzi, and P. Torricelli. 1984. Epidemiological study on workers exposed to low dimethylformamide concentrations. Giornale Italiano di Medicina del Lavoro, 6: 149-156.

Fiorito, A., F. Larese, S. Molinari and T. Zanin. 1997. Liver function alterations in synthetic leather workers exposed to dimethylformamide. Scandinavian Journal of Work, Environment and Health, 16: 289-292.

Attachment A

Managing Potential Conflicts of Interest

ITER Peer Review Meeting

February 14, 2000

(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 potential reviewers and more information on the *ITER* peer review program are available at http://www/tera/org/peer. Additional, *ad hoc* reviewers may be 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 assessments of ethylene glycol, dimethylformamide, and/or Health Canada, the sponsor of these discussions. 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. At the March 29 conference call, the reviewers verbally confirmed that their original statements regarding conflict of interest had not changed.

Mohamed S. Abdel-Rahman - Dr. Abdel-Rahman is on the faculty of the New Jersey Medical School, Department of Pharmacology and Physiology. He does not have any conflicts and will participate fully in all discussions and polling for consensus.

Charles Abernathy – Dr. Abernathy is a scientist with the U.S. Environmental Protection Agency's Office of Water. Dr. Abernathy is representing his own opinions and not that of his employer. He has no conflicts and will participate fully in all discussions and polling for consensus.

John Christopher - Dr. Christopher is a Staff 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."

James J. Collins – Dr. Collins is Director of Epidemiology with Solutia, Inc. He has no conflicts and will participate fully in all discussions and polling for consensus.

Joan T. Colman -- Dr. Colman is a scientist with Syracuse Research Corporation. She has no conflicts and will participate fully in all discussions and polling for consensus.

Moiz Mumtaz - Dr. Mumtaz is a scientist with the Agency for Toxic Substances and Disease Registry of the Centers for Disease Control. He has no conflicts and will participate fully in all discussions and polling for consensus.

Kenneth A. Poirier – Dr. Poirier is a scientist with Toxicology Excellence for Risk Assessment (*TERA*). Dr. Poirier will serve as panel chair. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

John Whalan – Mr. Whalan is a scientist with the U.S. Environmental Protection Agency's Office of Pesticide Programs, Health Effects Division. He has indicated that dimethylformamide is a registered inert solvent used in pesticide formulations; however, he has had no dealings with this chemical. The panel agreed that this does not create a conflict, Mr. Whalan will participate fully in all discussions and polling for consensus. Mr. Whalan, like the other reviewers, is representing his own opinions and not that of his employer.