ITER Peer Review on Phenol & Acetaldehyde Meeting Summary

ITER Peer Review Meeting Summary
September 30, 1997 University of Cincinnati, College of Medicine Cincinnati, Ohio USA

Assessments for phenol and acetaldehyde were reviewed by a panel of risk assessment experts on September 30, 1997. This meeting was convened 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 peer review meeting began with a discussion of conflict of interest. Prior to the meeting each reviewer certified that he or she did not have a conflict (real or apparent) for each assessment and sponsor. Possible conflicts were discussed with the reviewer (and the *TERA* Board of Trustees, as needed) to determine if measures were needed to manage the conflict (or appearance). Options include excluding the reviewer from that chemical's discussion and consensus, or allowing the reviewer to participate in the discussion but not be polled for consensus. The peer review panel discussed and agreed upon how to manage any potential conflicts. This is documented in Attachment A.

Phenol Assessment

Sponsor: Health Canada

Presenters: Ms. Wendy Dormer and Ms. Bette Meek, Health Canada

Chair: Dr. Michael Dourson, *TERA*

Review Panel:

- Dr. Matthew S. Bogdanffy, DuPont Haskell Laboratory
- Dr. Michael L. Dourson, Toxicology Excellence for Risk Assessment
- Ms. Annie Jarabek, U.S. EPA, National Center for Environmental Assessment *
- Dr. Russell E. Keenan, ChemRisk Division of McLaren/Hart
- Dr. George Leikauf, University of Cincinnati, Department of Environmental Health
- Dr. Randall Manning, Georgia Department of Natural Resources
- Dr. Edward Ohanian, U.S. EPA, Office of Water
- Dr. Kenneth A. Poirier, The Procter & Gamble Company
- Dr. Andrew Renwick, University of Southampton, Clinical Pharmacology Group
- Dr. Laura M. Rosato, Millennium Petrochemical Corporation
- Dr. Lawrence P. Sirinek, Ohio EPA, Division of Emergency and Remedial Response

*Ms. Jarabek was not able to attend the meeting in person but sent written comments for the panel and sponsor's consideration.

Presentation

Phenol (C6H6O) is a common industrial chemical used in the production and manufacture of many products. In general, the principal medium of exposure for the general population is food, although air contributes substantially to exposure in the vicinity of point sources. In addition to environmental exposures, phenol is produced endogenously by bacteria in the human gastrointestinal tract.

Health Canada presented an assessment of phenol including the derivation of a Tolerable Daily Intake (TDI) for oral non-cancer effects. Phenol is acutely toxic following both oral and dermal exposure and irritates the skin and mucous membranes. Non-neoplastic effects reported in exposed humans include haematological effects, increased hepatic serum enzymes, and suppression of immune response. The data are inadequate to assess the carcinogenicity of phenol in humans.

In laboratory animal studies, phenol decreased body weight gain and caused histopathological effects in the kidney, liver and thymus; myocardial necrosis; haematological effects; suppressed immune response; and neurological effects. Developmental toxicity of phenol has been reported at maternally toxic doses in several studies. In one study, decreased foetal weights were observed in rats at doses that did not generate maternal toxicity. In an early bioassay, there was no clear evidence of carcinogenicity in rats and mice; however, phenol does appear to act as a moderate promoter at toxic doses in mouse skin. In vitro assays indicate phenol may be weakly clastogenic. Although dose-response has been best characterized for developmental toxicity, some early sub-chronic studies and more recent short-term studies indicate that other end points may be more sensitive indicators of phenol toxicity. Health Canada considered the histopathological effects on the kidney in the Berman et al. (1995) study as critical, although possible immunological effects in the Hsieh et al. (1992) study were also noted.

Available subchronic and chronic studies following oral administration are limited and there are no recent studies in which a wide range of effects have been examined. NCI (1980) reported the only adverse effects in mice and rats exposed both chronically and subchronically were decreases in body weight gain at high doses (NOAELs of 100 mg/kg bw/day and greater). A wide range of tissues was examined for histopathological effects in these studies. In an early study, histopathological effects in the kidney were observed at 50 mg/kg bw/day (Dow, 1944).

In a more recent short-term study with histopathological examination of the liver, kidney, spleen, thymus and adrenals, non-significant increases in histopathological changes in the kidney were observed at 40 mg/kg bw/day administered by gavage in water to rats (Berman et al., 1995). This study also reported non-significant increases in thymic necrosis at 12 and 40 mg/kg bw/day. In a 4-week study by Hsieh et al. (1992) immune

response, as measured by a number of parameters, was suppressed at doses of 6.2 mg/kg bw/day and higher, though there were no gross lesions or weight changes observed in the spleen or thymus at doses up to 34 mg/kg bw/day (histopathological examination was not conducted).

Health Canada proposed a Tolerable Daily Intake (TDI) of 0.024 mg/kg bw/day, based on a NO(A)EL of 12 mg/kg bw/day for histopathological effects on the kidney in the Berman et al. (1995) study. This effect level was divided by an uncertainty factor of 500 for intraspecies variation (10), interspecies variation (10) and limitations of the database (5).

Health Canada found it difficult to dismiss the results of the short-term studies, even in light of the long-term study results. They sought the panel's opinions as to the significance of these findings and appropriateness of their use. They also requested opinions on the magnitude of the database uncertainty factor and whether more meaningful conclusions could be drawn from comparison with compounds such as benzene, for which phenol is a principal metabolite.

The presenters noted that the phenol supporting documentation underwent peer review within Health Canada and was externally reviewed for adequacy of coverage by industry scientists. In addition, BIBRA International reviewed the supporting documentation and risk assessment.

Hazard Identification

The discussion centered on the lack of recent chronic and multiple end point studies for development of a risk value for phenol and on the significance of the more recent short-term studies which show effects which were either not examined or not noted in the earlier studies. The panel agreed that there are sufficient data to assess the non-cancer effects.

The significance of effects on the immune system as reported by Hsieh et al. (1992) was discussed at length. Reviewers identified several inconsistencies in the data. One reviewer noted that stress has profound effects on immune response in mice and many of the results in the paper might be explained by this. Questions were also raised about the actual doses received by the test animals in the high dose group. Based on the estimated doses, water consumption in the high dose groups appeared greater than normal for this type of animal study. The decreased RBC with no corresponding decrease in hematocrit was questioned. It was speculated that water spillage may have occurred due to taste aversion; and the animals may in fact have been volume depleted.

Questions about the clinical significance of these immunological findings were also raised. One reviewer pointed out that it is unlikely that the immunological changes in Hsieh et al. (1992) would be associated with adverse clinical manifestations. The assays used in this study were rather crude. More recent studies would use more sensitive assays. The panel concluded that although the current study provides only weak evidence

for immunotoxicity (findings may be a stress response), and the clinical significance of the findings is limited, evidence is sufficient to warrant further investigation of potential effects of phenol on the immune system. Health Canada indicated that they understand CMA (Chemical Manufacturers Association) is considering covering immunological end points in its study.

Health Canada identified histopathological effects in the kidney as the critical effect for the assessment. The proposed TDI is based on the Berman et al. (1995) study in which 3 of 8 animals showed signs of kidney damage after 14 days gavage treatment at 40 mg/kg bw/day. This was not statistically significant at the 5% level, however, with group sizes limited to 8 animals the statistical power of the study is fairly low. The panel noted that the Dow (1944) chronic toxicity study also reported kidney effects at 50 mg/kg bw/day via gavage.

The panel discussed the potential role different routes of administration play in the disparity in results between the NCI (1980) drinking water and Dow (1944) gavage studies. The Health Canada assessment document discusses that the difference in the LO(A)ELs (Low Observed [Adverse] Effect Levels) in these studies may be explained in part by route of administration, which would be consistent with the pharmacokinetic data. One reviewer commented that based on the Dow (1994) study it appears that phenol administration in a bolus dose saturates the sulfate conjugation pathway at 150 mg/kg bw/day, but not at 15 mg/kg bw/day. The NCI drinking water study high dose group of 10,000 ppm (estimated 380 mg/kg bw/day) would also have been a saturating dose, yet no renal effects were observed. Thus, the route of administration may not adequately explain the variable results between these studies.

One panel member sought clarification about the way the Berman et al. (1995) paper grouped incidence of renal tubular necrosis, protein casts and papillary hemorrhage together. Ms. Dormer clarified that the IPCS (International Programme on Chemical Safety, 1994) document noted that two animals had tubular degeneration and one animal had protein casts in the tubules. The IPCS cited personal communication with an author as the source for this information. Another panel member added that the Dow study showed 2 of 6 animals had kidney effects at the LOAEL of 50 mg/kg/day.

Developmental toxicity is another end point of concern for phenol. Health Canada indicated that the assessment of developmental toxicity has not changed in recent years, with the exception of the Narotsky and Kavlock (1995) paper in which effects (including maternal toxicity) were observed at lower doses than the earlier developmental toxicity studies. It was concluded that renal effects remain the critical effect since the documented developmental effects occur at higher doses.

Neurological effects were also discussed, including the Hsieh et al. (1992) and Moser et al. (1995) studies. The panel agreed that the results were not useful for defining the critical effect.

Dose-Response Assessment

Choice of Dose: The panel agreed that the kidney is the critical end point and that 12 mg/kg bw/day reported by Berman et al. (1995) is a clear NOEL (No Observed Effect Level). Health Canada originally qualified its choice of the 12 mg/kg bw/day NOEL, citing the immunological responses at lower levels in the Hsieh et al (1992) study. The panel agreed that it would be premature to base the TDI on immunotoxicity, as the response in Hsieh et al. (1992) may be due to stress, inconsistencies exist among some of these tests, and the clinical significance of the observed effects is questionable. However, future study of this end point would be useful.

The Chair solicited comments from the group about identifying the 40 mg/kg bw/day as a LOEL (Low Observed Effect Level) based on renal effects. The panel agreed that a dose of 40 evokes a response, it is not clear whether the effects are adverse or not, due to study design limitations. Health Canada indicated that they consider 40 to be a LOEL (or perhaps a NOAEL [No Observed Adverse Effect Level], since there was an increase at this level, but it was non-significant). Health Canada acknowledged that it is difficult to put the 40 dose level "in a box" and they prefer to qualify the identification of the effect level with a discussion. The Chair summarized the panel's agreement that identifying 40 mg/kg/day as a LOEL is conservative because the increase was not statistically significant (there was a small number of animals per dose group and the effects were minor). This dose is also in the range where saturation of the sulfate conjugation pathway occurs.

Given the conservatism of the 40 mg/kg bw/day as a LOEL, Health Canada agreed that they would emphasize in their document the degree of conservatism in labeling the 12 mg/kg bw/day dose as a NOEL.

Uncertainty Factors: Health Canada provided a brief overview on the selection of uncertainty factors in their methodology (Meek et al., 1994). Default uncertainty factors of 10 are generally used for intra- and interspecies variability; however, these can be replaced with data-derived factors when appropriate data are available. A factor of 1 to 100 is considered for the remaining uncertainties in the data base. These are grouped together to avoid "double counting" of the same area of uncertainty. The option of using less than 10 is available, with a value of five traditionally chosen.

Intra-and Interspecies: The panel considered the uncertainty factors, beginning with the proposed 10-fold factor for intraspecies variability. The panel discussed whether the available data are sufficient to assign a less than default value. One reviewer indicated that the existing data are metabolism studies that do not provide sufficient information on kinetics to assess interindividual variability.

The panel discussed human variability in sulfyltransferase activity. One panel member indicated that perhaps a half log variability is observed, but the oxidation activity by the CYP2E family has tremendous variability. Therefore, there is significant potential for intra-human variability, so that departure from the default value is not warranted. Another reviewer proposed that the kinetics portion of this UF be lowered to 1 since the proposed TDI is well below saturating doses. This would lead to a total UF of 3 for intraspecies

variability. Other reviewers disagreed, with one stating that setting it at 1 implies no intra-human variability. The data are also not clear on whether free phenol or a metabolite is the toxicant. The panel agreed that the current data do not allow for replacing the default uncertainty factor.

The panel then discussed the proposed value of 10 for interspecies variability. The panel agreed that this factor of 10 is conservative (health protective) for a number of reasons. For example, if the oxidative metabolism of phenol generates an active metabolite, then comparison between rats and humans (Capel et al., 1972 data) suggests a 20-fold higher dose of the putatively toxic metabolite (which has not been identified with certainty) compared to humans. While the panel agreed that there are not sufficient data to use other than the 10-fold default factor for interspecies variability this is an area in which new studies might make an impact on modification of the TDI for phenol.

Data Deficiencies: The uncertainty factor of 5 for limitations in the database was discussed. Health Canada indicated that the factor of 5 was proposed because of the possibility of low dose effects not being detected in the current short-term studies, particularly possible hematological effects. The key question is whether additional studies would identify effects not seen in the currently available data. The Chair asked what studies would be required to eliminate the need for this factor. Health Canada stated that they would like to see a more recent longer-term repeated dose toxicity study, which evaluates multiple endpoints including immunological and hematological.

The panel was asked whether there is additional uncertainty that has not already been addressed. Several reviewers questioned whether the factor of 5 is needed since the NOEL is based on a gavage study which is probably conservative. Several reviewers were uncomfortable with any effort to adjust the uncertainty factors in response to a discomfort with the NOEL. Health Canada indicated that they chose the NOEL of 12 mg/kg bw/day because it is a clear NOEL, while the 40 mg/kg bw/day is less clear as a LOEL.

It was pointed out, and briefly discussed, that the proposed TDI is only 20% of the normal endogenous production of phenol by humans in the gastrointestinal tract. The reviewers compared the endogenous rate of phenol production in humans (10 mg/day or 0.14 mg/kg bw/day for a 70 kg human) to rats [approximately 0.5 mg/day or 0.8 mg/kg bw/day (Lawrie and Renwick, 1987)]. One reviewer commented that while it appears that the resulting exposure of a target organ to endogenous production is lower in humans than animals, we do not know how to account for this. The panel recognized that while this is an issue, there is no way to address this in the TDI. Several reviewers also noted that we do not know that the endogenous phenol is without effect. It was noted that endogenous production is an issue for a number of compounds, however, small additions to endogenous doses cannot be assumed to be without effect (carbon monoxide was mentioned as an example).

One reviewer suggested waiting until the CMA data are available to finalize the assessment, but another pointed out that there are frequently outstanding studies and

agencies cannot always wait for these results to make a decision. Health Canada indicated that while their regulatory time commitments for these assessments preclude waiting for additional studies, there are mechanisms for reassessments which are decided on a case-by-case basis. Health Canada indicated that they must move forward at this time, but that assessments are a "snapshot in time."

Health Canada indicated that they would not have difficulty revising their original proposal due to the judged lack of significance of the immunological changes reported at doses similar to and lower than 12 mg/kg bw/day. While one or two reviewers thought Health Canada's original proposal of a NOEL of 12 mg/kg bw/day and a UF of 500 was still the best choice, most of the reviewers supported either using the NOEL of 12 mg/kg bw/day and a UF of 100, with caveats about uncertainties in the database; or using a LOEL of 40 mg/kg bw/day and maintain the originally proposed UF of 500. The resulting TDIs are very similar. Health Canada preferred this dual approach and indicated they would move forward with both and identify the types of studies needed to reduce uncertainty.

Recommendations

* Present at least the two approaches: a NOEL of 12 mg/kg bw/day and a UF of 100, with caveats about uncertainties in the database; and a LOEL of 40 mg/kg bw/day with the originally proposed UF of 500.

* Though available data do not warrant consideration of immunological effects as co-critical, currently, additional investigation in this area is recommended.

References

Berman, E., M. Schlicht, V. Moser, and R. MacPhail. 1995. A multidisciplinary approach to toxicological screening: I. Systemic toxicity. J. Toxicol. Environ. Health 45: 127-143.

Capel, I., M. French, et al. 1972. Fate of [14C]-phenol in various species. Xenobiotica 2:25- 34. Dow Chemical Company. 1994. Pharmacokinetics, metabolism and distribution of 14C-Phenol in Fischer 344 rats after gavage, drinking water and inhalation exposure. Hiser, M.F., Kroposcott, B.E., McGuirk, R.J., and Bus, J.S., Toxicology Research Laboratory, Dow Chemical Company, Midland, Michigan, June 14, 1994 (unpublished).

Dow Chemical Company. 1944. The toxicity of phenol. Unpublished manuscript by E.M. Adams, Biochemical Research Laboratory, Dow Chemical Company.

Hsieh, G.C., R. Sharma, R. Parker, and R. Coulombe, Jr. 1992. Immunological and neurobiochemical alterations induced by repeated oral exposure of phenol in mice. Eur. J. Pharmacol. Environ. Toxicol. Pharmacol. Sect. 228:107-114.

IPCS. 1994. Environmental Health Criteria 161: Phenol. International Programme on Chemical Safety, World Health Organization, Geneva, 151 pp.

Kavlock, R.J. 1990. Structure-dosimetry-activity relationships in the developmental toxicity of substituted phenols: in vivo effects. Teratology 41:43-59.

Lawrie, C.A., and Renwick, A.G. 1987. The effect of saccharin ingestion on the excretion of microbial amino acid metabolites in rat and man. Toxicol. Appl. Pharmacol. 91: 415-428.

Meek, M.E., R. Newhook, R.G. Liteplo and V.C. Armstrong. 1994. Approach to Assessment of Risk to Human Health for Priority Substances under the Canadian Environmental Protection Act. Environ. Carcino. & Ecotox. Revs., C12(2), 105-134.

Moser, V.C., B. Cheek and R. MacPhail. 1995. A multidisciplinary approach to toxicologial screening: III. Neurobehavioural toxicity. J. Toxicol. Environ. Health 45: 173-210.

NCI. 1980. Bioassay of Phenol for Possible Carcinogenicity. Carcinogenesis Testing Program, National Cancer Institute/National Toxicology Program (NCI-CG-TR-203: NTP No. 80-15). US Department of Health and Human Services, Bethesda, Maryland.

Schlicht, M., V. Moser, B. Sumrell, E. Berman and R. MacPhail. 1992. Systemic and neurotoxic effects of acute and repeated phenol administration. Toxicologist 12:274 (Abstract No. 1047).

Acetaldehyde Assessment

Sponsor: Health Canada

Presenters: Ms. Rose Gomes and Ms. Bette Meek, Health Canada

Chair: Dr. Michael Dourson, TERA

Review Panel:

- Dr. Karen Blackburn, The Procter & Gamble Company
- Dr. Matthew S. Bogdanffy, DuPont Haskell Laboratory
- Dr. Michael L. Dourson, Toxicology Excellence for Risk Assessment
- Ms. Annie Jarabek, U.S. EPA, National Center for Environmental Assessment *
- Dr. Russell E. Keenan, ChemRisk Division of McLaren/Hart
- Dr. George Leikauf, University of Cincinnati, Department of Environmental Health
- Dr. Randall Manning, Georgia Department of Natural Resources
- Dr. Edward Ohanian, U.S. EPA, Office of Water
- Dr. Kenneth A. Poirier, The Procter & Gamble Company
- Dr. Andrew Renwick, University of Southampton, Clinical Pharmacology Group
- Dr. Laura M. Rosato, Millennium Petrochemical Corporation

- Dr. Lawrence P. Sirinek, Ohio EPA, Division of Emergency and Remedial Response

*Ms. Jarabek was not able to attend the meeting in person but sent written comments for the panel and sponsor's consideration.

Presentation

Acetaldehyde (C_2H_4O) is a chemical intermediate used primarily in the manufacturing of acetic acid. It is also used in the manufacturing processes for plastics, rubbers, resins, dyes, varnishes, fragrances and room-deodorizers. It has been labeled as GRAS (generally recognized as safe) for uses as a flavour additive and adjuvant. It is also used as a post-harvest fumigant for fruit. Principal sources of human exposure to acetaldehyde include foodstuffs, indoor air, and cigarette smoke.

Health Canada presented noncancer and cancer inhalation assessments for acetaldehyde. Information was presented first on the hazard identification of both noncancer and cancer endpoints; this was followed by a presentation on dose-response relationships for each.

Early studies in humans have reported irritation and cardiovascular effects in clinical studies of humans exposed to acetaldehyde. There is only one epidemiological study, which is inadequate for use in risk assessment. It was noted, however, that long-term exposure of humans to acetaldehyde is likely to be limited by respiratory tract and ocular irritation, which has been noted at concentrations of 25 ppm or more.

In laboratory animals, effects are also elicited at the portal-of-entry; specifically, hyperkeratosis of the forestomach is seen following oral exposure, and lesions in the upper respiratory tract are seen following inhalation exposure. There are no data on reproductive, developmental, neurological, or immunological effects, but it was noted by Health Canada that systemic effects are not likely to be of concern for acetaldehyde following inhalation exposure because it is so rapidly metabolized in the upper respiratory tract.

In addition to the noncancer effects, acetaldehyde has also been shown to cause an increased incidence of tumours in the upper respiratory tract of rats and hamsters at concentrations that also cause cytotoxicity. Health Canada reported that acetaldehyde has been shown to be genotoxic both in vitro and in vivo, causing mutagenic, clastogenic and aneugenic effects. An increase in DNA-protein-crosslinks has also been noted in rat nasal epithelium at tumourigenic concentrations.

For noncancer effects, there are two studies which Health Canada considered to be co-critical: the two 4-week inhalation studies in Wistar rats by Appelman et al. (1982 and 1986). Although longer-term studies are available, they were conducted only at higher concentrations; these shorter-term studies were considered to provide the best characterization of the dose-response relationship for acetaldehyde. The study by Appelman et al. (1986) identified a No-Observed-Effect-Level (NOEL) of 150 ppm (270

mg/cu.m) acetaldehyde, and the study by Appelman et al. (1982) identified a Lowest-Observed-Effect-Level (LOEL) of 400 ppm (720 mg/cu.m) based on degenerative effects in the nasal olfactory epithelium.

A benchmark concentration associated with a 5% incidence of effects (BMC-05) of 357 mg/cu.m was calculated. This was based on combined data from the studies by Appelman et al. (1982 and 1986); modeling was done using the THRESH program.

Health Canada developed Tolerable Concentrations (TCs) based on the NOEL of 270 mg/cu.m and the BMC-05 of 357 mg/cu.m. Each concentration was adjusted for intermittent to continuous exposure by multiplying by 6 hr/24 hr and 5 days/7 days (a factor of 0.18), resulting in adjusted concentrations of 48.6 and 64 mg/cu.m, respectively. An uncertainty factor of 100 was applied to account for inter- and intra-species extrapolations. The TC was determined to be 0.49 mg/cu.m (490 ug/cu.m) based on the NOEL, and 0.64 mg/cu.m (640 ug/cu.m) based on the BMC-05.

For cancer, an increase in nasal tumours in rats and laryngeal tumours in hamsters have been noted, but only at doses which are also associated with cytotoxicity. The critical study for carcinogenicity is Woutersen et al. (1986), a lifetime inhalation bioassay in Wistar rats, which are more sensitive than hamsters to acetaldehyde. The Tumourigenic Concentration-05 (TC-05) was calculated based on nasal carcinomas and adenocarcinomas in male rats. As with the noncancer assessment, the experimental concentrations were adjusted for intermittent to continuous exposure by multiplying by 6 hr/24 hr and 5 days/7 days. The TC-05 was calculated to be 86 mg/cu.m.

During the presentation, Health Canada listed the following four issues for consideration by the peer review panel:

* How to address carcinogenicity in view of limited mechanistic data?* Is it appropriate to incorporate an intermittent to continuous dosing conversion factor for the tolerable concentration?

* Have inadequacies of the database been adequately addressed, in view of the fact that site of entry effects are limiting?

* Can any more meaningful conclusions be drawn based on more complete comparison with formaldehyde?

NONCANCER ASSESSMENT

Hazard Identification

The panel agreed with Health Canada that portal-of-entry effects represent the critical effect following inhalation exposure to acetaldehyde. One reviewer indicated that it would be good to better characterize target tissue doses for different species, because the rat appears to be the most sensitive species based on experimental concentrations, but that

a more accurate determination of species' sensitivities should be based on target tissue doses. Another reviewer indicated that data are available to show that at low concentrations of acetaldehyde, deposition in the upper respiratory tract of rats and hamsters is comparable. At higher concentrations, deposition in hamsters may be slightly higher, but the difference is not appreciable. It was agreed that the rat is, in fact, the more sensitive of the two species.

The panel agreed that the studies by Appelman et al. (1982 and 1986) should serve as co-critical studies for the noncancer assessment.

Dose-Response Assessment

Choice of Dose: The peer review panel agreed that the experimental concentration of 150 ppm (270 mg/cu.m) acetaldehyde identified by Appelman et al. (1986) is a NOEL, and the experimental concentration of 400 ppm (720 mg/cu.m) acetaldehyde identified by Appelman et al. (1982) is a LOEL based on degenerative effects in the nasal olfactory epithelium.

With regard to the BMC-05 calculation, Health Canada agreed with the written comments provided by one reviewer indicating that the parameter estimates and goodness-of-fit statistics should be added to the report.

One reviewer noted that the full report on the 2-year rat bioassay (Woutersen et al., 1986) is available under TSCA (Toxic Substances Control Act). While an evaluation of the full report may be of value for the sake of completeness, the peer review panel agreed with Health Canada that it will not affect the bottom line of this risk assessment.

One of the issues specifically identified by Health Canada for discussion by the panel was whether it is appropriate to adjust the intermittent exposure concentration by 6/24 and 5/7 to achieve a continuous exposure concentration. This is referred to here as the CxT issue and refers to whether health effects are related to exposure concentration or cumulative exposure.

One reviewer asked whether thiol depletion is an issue; that is, if the animal has 18 hours/day to recover and replenish thiol stores, versus being exposed continuously, is this likely to affect the dose-response relationship? Another reviewer indicated that in his experience, thiol depletion occurs to some extent, but is not of toxicological concern. Rather, formation of acetic acid, and the resulting cytotoxicity may be more important. This is suggested by experiments in isolated rat nasal epithelial cells, in which cytotoxicity was observed following exposure to acetic acid, but not acetaldehyde. However, this is strictly concentration-dependent, with rapid repair and compensation also taking place. This reviewer thought that a CxT adjustment of 6/24 and 5/7 is likely to be overly conservative and should be "scaled down" or not used at all.

One reviewer asked whether benchmark modeling was done for the 2-year study (Woutersen et al., 1986) or only for the 4-week studies. Health Canada indicated that the

two-year bioassay was evaluated qualitatively, but that quantitative modeling was not done due to the limited number of concentration levels and observation of effects in all groups.

Although this remains an area for future research, the peer review panel agreed with the Health Canada conclusion that there are currently no data to deal directly with the CxT issue. The discussion about modeling the data from the 2-year bioassay are not likely to help with this issue because this study also utilized a 6 hours/day and 5 days/week exposure protocol. Health Canada also looked at information from studies using formaldehyde, but determined that the data were not informative with respect to effects of intermittent versus continuous exposure. The peer review panel, therefore, agreed that it is appropriate to make the CxT adjustment as was presented by Health Canada, based on the lack of data on effects in similar strains at similar concentrations following continuous versus intermittent exposure.

Uncertainty Factors: The panel discussed the selection of uncertainty factors.

Intra- and Inter-species: An uncertainty factor (UF) of 100 was proposed for intraspecies variation (10-fold) and for interspecies extrapolation (10-fold).

One reviewer asked whether 10-fold was sufficient for intraspecies variation, given the known polymorphism for aldehyde dehydrogenase, which may argue for a 30-fold UF. Health Canada indicated that these data are for aldehyde dehydrogenase levels in the liver, and we have no way of knowing how that compares with the distribution of enzyme activity in the nasal epithelium. In a later discussion, one reviewer stated that we also do not know whether lower levels of aldehyde dehydrogenase are likely to make an individual more susceptible (because there will be more genotoxic activity associated with the unmetabolized parent compound), or whether it might actually be protective (because there will be less cytotoxicity associated with acetic acid formation). Following a discussion of the complexity of this issue, the panel agreed that a 10-fold factor was most appropriate for intraspecies variation. A factor of 10 was also proposed for interspecies extrapolation. One reviewer suggested that this is a very conservative position because it does not take into account anatomic differences between species. In specific, there is greater penetration of inhaled gases into the lower airways of humans as compared with rodents, so that the dose is distributed over a larger surface area. Since the toxic effects of acetaldehyde are mediated by the dose reaching target cells in the upper respiratory tract, humans are likely to be less sensitive than rodents to the induction of nasal lesions. After some discussion of this issue, it was agreed that species-specific target tissue doses cannot be quantified (unless a PBPK model were available), and that it is appropriate to use the default value of 10 until more information is available to support a different number. It was suggested that Health Canada add text to indicate that this is a conservative, health-protective assumption.

Data Deficiencies: Although the critical studies were only 4 weeks in duration, no additional UF was recommended by Health Canada for extrapolation from a subchronic to chronic exposure. A factor was not considered to be necessary specifically because the

experimental exposure concentrations had already been adjusted for intermittent-to-continuous exposures, and this is likely to be overly conservative. Also, there is no indication that the severity of the critical effect increases with the duration of exposure. The peer review panel agreed with this assessment.

In written comments, one reviewer indicated that a partial UF may be warranted for database deficiencies, particularly because it is known that acetaldehyde can cross the placenta and is potentially fetotoxic. As a whole, the group felt that systemic toxicity, including any effects on a fetus, are not likely to be of concern following inhalation exposure to acetaldehyde, as exposure is likely to be limited by respiratory tract and ocular irritation. It was agreed that an additional factor for developmental effects was not necessary.

In summary, the peer review panel agreed that a total UF of 100-fold was appropriate to account for intraspecies and interspecies extrapolations. Applying the 100 UF to the NOEL of 270 mg/cu.m (after adjusting the NOEL to a continuous exposure concentration of 48.6 mg/cu.m) results in a TC of 0.49 mg/cu.m (490 ug/cu.m). Applying the 100 UF to the BMC-05 of 357 mg/cu.m (after adjusting the BMC-05 to a continuous exposure concentration of 64 mg/cu.m) results in a TC of 0.64 mg/cu.m (640 ug/cu.m). The peer review panel agreed that these calculations were done appropriately.

With regard to the issues listed by Health Canada for consideration by the peer review panel, three pertained to the noncancer assessment. The consensus of the group was as follows:

* Is it appropriate to incorporate an intermittent to continuous dosing conversion factor for the tolerable concentration? The peer review panel agreed that this is appropriate. Although it was felt that this is likely to be a conservative assumption, data are not available to support a different quantitative analysis.

* Have inadequacies of the database been adequately addressed, in view of the fact that site of entry effects are limiting? The peer review panel agreed that the inadequacies of the database been adequately addressed. One reviewer suggested that further evaluation of the full report of the 2-year bioassay by Woutersen et al. (1986) might alleviate any remaining concerns for systemic effects (which were expressed in written comments from one reviewer, particularly over concern for whether there is any potential developmental effects). The panel agreed, however, that although this might increase confidence, it was unlikely to have an impact on the overall assessment, since based on available data, appreciable systemic doses are not expected.

* Can any more meaningful conclusions be drawn based on more complete comparison with formaldehyde? The panel agreed with Health Canada that while it might be worth mentioning the research that has been done on the airflow modeling and induction of DNA-protein crosslinks for formaldehyde (which highlights the significance of anatomical differences between species in determining target tissue doses), there are no data from the formaldehyde assessment that can be specifically applied to acetaldehyde.

Recommendations

As a whole, the peer review panel thought that the assessment presented by Health Canada reflects the best science currently available for acetaldehyde. Minor suggestions, reflected in these summary notes, were offered, but it is noted that these are not likely to have an impact on the outcome of the assessment.

CANCER ASSESSMENT

Hazard Identification

The peer review panel agreed that acetaldehyde is carcinogenic in laboratory animals at the point of contact (i.e., in the upper respiratory tract following inhalation exposure). Nasal tumors are induced in rats and laryngeal tumors in hamsters.

The group did not discuss the specific classification of acetaldehyde with regard to carcinogenicity, but focused on the dose-response assessment.

Dose-Response Assessment

The peer review panel agreed that the only epidemiological study on acetaldehyde is insufficient for use in risk assessment, so that the quantitative estimate should be based on an animal bioassay.

Woutersen et al. (1986) conducted the only chronic bioassay in Wistar rats, which are more sensitive than hamsters to the carcinogenic effects of acetaldehyde. As with the noncancer assessment, the intermittent exposure concentrations were adjusted by 6/24 and 5/7 to give the equivalent concentrations for a continuous exposure. Based on the combined incidence of nasal carcinomas and adenocarcinomas in male rats (which were shown to be more sensitive than females), a Tumourigenic Concentration at the 5% level (TC-05) was calculated to be 86 mg/cu.m. The main point of discussion regarding the cancer assessment for acetaldehyde focused on whether there is sufficient evidence to show that the carcinogenicity is mediated by the cytotoxicity which is induced by acetaldehyde. One peer reviewer indicated that it was his belief that if you protect against cytotoxicity, then you have also protected against carcinogenicity, since the former is necessary for the latter. He suggested that it was appropriate to provide only one assessment which covers both endpoints.

The position taken by Health Canada on this issue is summed by their statement that "it is possible that the cytotoxicity of acetaldehyde at high concentrations is the crucial determinant in the carcinogenesis of this compound observed at the site of exposure and that tolerable concentrations developed to protect against non-neoplastic effects in the upper respiratory tract may also be protective for cancer. However, in view of the documented genotoxicity of acetaldehyde and the relative lack of information on the mechanism of induction of tumours for this compound, an estimate of the carcinogenic potency has also been derived..."

The peer reviewers did a side-by-side comparison of the BMC-05 for noncancer effects (64 mg/cu.m) and the TC-05 for cancer (86 mg/cu.m) and agreed that both effects are clearly seen in the same dose range. Because Health Canada does not use low-dose extrapolation methods for cancer endpoints, it makes less difference whether one uses a single assessment (the BMC-05) in protecting against both cancer and noncancer endpoints. Regardless, from a philosophical view point, Health Canada maintains that there is still insufficient information to definitively conclude that the cytotoxicity is the sentinel effect resulting in carcinogenicity, and that it is best to maintain both assessments. The peer review panel agreed. It was also suggested that if this assessment were to be loaded onto *TERA's ITER* database, it would not be appropriate to use linear extrapolation procedures to aid in the comparison of Health Canada's TC-05 with EPA's cancer assessment because the risk below the TC-05 will fall off dramatically because of the highly nonlinear dose-response relationship for acetaldehyde.

Recommendations

* Health Canada may want to present a table with a side-by-side comparison of the NOAEL, BMC and TC-05 values.

References

Appelman, L.M., R.A. Woutersen and V.J. Feron. 1982. Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology 23: 293-307.

Appelman, L.M., R.A. Woutersen, V.J. Feron, R.N. Hooftman and W.R.F. Notten. 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol. 6(5): 331-336.

Woutersen, R.A., L.M. Appelman, A. van Garderen-Hoetmer and V.J. Feron. 1986. Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology 41: 213-231.

Attachment A Managing Potential Conflicts of Interest

TERA 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. However, individual peer reviewers are representing their own expertise and views, not those of their employer.

TERA requested that each peer reviewer identify potential conflicts of interest related to the review of health risk assessments of acetaldehyde and phenol. Each reviewer signed a statement indicating that he or she does not have a conflict of interest concerning these chemicals; with the comments noted below. *TERA* discussed these potential conflicts with the individuals involved and a *TERA* trustee. The panel accepted the following:

Karen Blackburn - Dr. Blackburn works for The Procter & Gamble Company which uses phenol in one of its health care products. She has requested not to participate in the review of phenol. She has no conflicts with acetaldehyde and will participate fully in that review.

Matthew S. Bogdanffy - Dr. Bogdanffy works for the Haskell Laboratory of DuPont. Dr. Bogdanffy is familiar with the acetaldehyde literature due to his research on the Vinyl Acetate Toxicology Group (vinyl acetate is metabolized to acetaldehyde). *TERA* does not think this is a conflict and recommends that Dr. Bogdanffy participate fully in the discussions and polling for consensus on both chemicals. The panel agreed.

Michael Dourson - Dr. Dourson works for Toxicology Excellence for Risk Assessment. He does not have any conflicts with the two chemicals and will participate fully in the reviews.

Annie Jarabek -- Ms. Jarabek works for the U.S. Environmental Protection Agency, Office of Research and Development. She does not have any conflicts with the two chemicals and could participate fully in the reviews. Ms. Jarabek was not able to attend the meeting and provided written comments for the panel's and sponsor's consideration. Because she will not benefit from the dialogue, she requests, and the panel agreed, that she would not take part in polling for consensus.

Russell Keenan - Dr. Keenan works for the ChemRisk Division of McLaren/Hart. He does not have any conflicts with the two chemicals and will participate fully in the reviews.

George Leikauf - Dr. Leikauf is with the University of Cincinnati, Department of Environmental Health. He does not have any conflicts with the two chemicals and will participate fully in the reviews.

Randall Manning - Dr. Manning works for the Georgia Department of Natural Resources. He does not have any conflicts with the two chemicals and will participate fully in the reviews.

Edward Ohanian - Dr. Ohanian works for the U.S. Environmental Protection Agency, Office of Water. He does not have any conflicts with the two chemicals and will participate fully in the reviews.

Kenneth Poirier -- Dr. Poirier works for The Procter & Gamble Company which uses phenol in one of its health care products. In a previous position with P&G, Dr. Poirier was involved in regulatory activities concerning phenol. As such, he has considerable knowledge about the chemical and its toxicity. *TERA* recommended that he participate in the discussion but not be polled for consensus. The panel agreed.

Andrew Renwick - Dr. Renwick is with the University of Southampton, Clinical Pharmacology Group. He does not have any conflicts with the two chemicals and will participate fully in the reviews.

Laura Rosato - Dr. Rosato works for Millennium Petrochemical Corporation. Dr. Rosato also participates on the Vinyl Acetate Toxicology Group (see Dr. Bogdanffy above). *TERA* does not see this as a conflict and recommends that Dr. Rosato participate fully in the discussions and polling for consensus on both chemicals. The panel agreed.

Lawrence P. Sirinek - Dr. Sirinek works for the Ohio Environmental Protection Agency, Division of Emergency and Remedial Response. He does not have any conflicts with the two chemicals and will participate fully in the reviews.