ITER Peer Review on Hexachlorobutadiene & Acrylonitrile Meeting Summary

September 19, 1996

Reviewers:

Dr. John Christopher, California EPA
Dr. Michael Dourson, *TERA*, Chair
Dr. Marvin Friedman, Cytec Industries, Inc.
Dr. Michael Gargas, ChemRisk Division of McLaren/Hart
Dr. Patricia McGinnis, Syracuse Research Corporation
Ms. Bette Meek, Health Canada
Dr. Edward Ohanian, U.S. EPA
Dr. Jon Reid, University of Cincinnati

Presenter:

Ms. Kathy Hughes, Health Canada

Review Process and Groundrules

The meeting began with a review of the process and the groundrules.

1. Reviewers will have thoroughly looked at premeeting packages sent to them 3 weeks ahead of time. Sponsors of chemical files will give an approximately 15 minute overview on the basis for the risk assessment value.

2. The presentation will be followed by questions and answers for approximately two hours. The question and answer session will be structured in the following way:

- Was the literature search complete? Is anyone aware of additional data not included?
- Did the assessment follow the specified method?
- Was the rationale for choice of critical effect, critical study, etc. appropriate?
- Is the resulting risk value appropriate?

3. Following questions and answers, an opportunity for technical comments from observers will be allowed.

4. Reviewers will be polled for consensus; consensus is defined from Websters as "the judgment arrived at by most of those concerned". Consensus categories for the risk assessment include acceptance as is or with minor comments, acceptance after issues are addressed, or non-acceptance due to major problems that preclude consensus.

5. A meeting summary will be written after each meeting. It will summarize major issues discussed and will be distributed to each reviewer for comment before being placed on *TERA'*s homepage.

6. It is not the purpose of these reviews to comment on the methods used for each assessment. Therefore, comments on methods will not be entertained. However, in special cases when requested by the sponsoring organization, such comments may be sought.

Reviewers raised some concern about the use of a standardized literature search strategy in preparing files for future peer review meetings. *TERA* has developed a standardized literature search strategy which will be distributed to sponsors/presenters in the future. The general feeling of reviewers was that if a file is prepared following this standardized strategy, then the results of the search will be adequate for this process.

Conflict of Interest Discussion

A Conflict of Interest statement was discussed and approved; this statement is appended to the meeting notes. It was noted that *TERA* relied upon AIHC and U.S. EPA guidelines in developing the *ITER* policy used to evaluate potential conflicts of interest for this meeting.

Concern was expressed that affiliation, as with a particular industry, not be used to eliminate knowledgeable people as reviewers. Participants felt that it is important to have the appropriate people reviewing a given document. As long as a reviewer does not use the peer review process to serve or further his or her own interests, then having an "affiliation" conflict should not preclude a reviewer from participating in the discussion. It is the Chairs job to monitor the discussion with this in mind. However, it is also appropriate that a reviewer with an "affiliation" conflict not participate in the polling for consensus

It was noted that there is a potential conflict for reviewers from government/regulatory agencies whenever the chemical in question is regulated by the agency. It was suggested that the *TERA* policy specifically address situations when a governmental regulator may have a conflict.

The participants discussed the potential conflicts of each individual reviewer and agreed to the conclusions of the attached statement.

Hexachlorobutadiene (HCBD) Presentation and Discussion

Kathy Hughes of Health Canada made a short presentation on the Health Canada assessment.

Hexachlorobutadiene (HCBD) is formed during the processing of other chemicals and is an intermediate in the manufacture of rubber compounds and lubricants. Little

information is available on the effects of hexachlorobutadiene (HCBD) in humans. In the available subchronic and chronic animal studies, the kidney has consistently been observed to be the most sensitive target organ.

In the only long-term study available, groups of Sprague-Dawley rats were administered doses of 0, 0.2, 2, or 20 mg/kg-bw/day in the diet for two years (Kociba et al., 1977). There was increased incidence of renal tubular hyperplasia/proliferation and an increase in levels of renal coproporphyrin at 2 mg/kg-bw/day HCBD and above. At the highest dose (20 mg/kg-bw/day), there was increased mortality in males, decreased body weight gain and increased relative and absolute kidney weights in both sexes, and an increased incidence of renal tubular adenomas and/or adenocarcinomas in both sexes.

In subchronic studies renal toxicity (renal tubular epithelial degeneration/ regeneration and necrosis) was observed at doses as low as 2 (rats) and 0.5 (mice) mg/kg-bw/day (Schwetz et al., 1977; Yang et al., 1989; NTP, 1991). The observation of renal tubular regeneration and severity of that lesion in one female mouse at the 0.2 mg/kg-bw/day dose (Yang et al., 1989; NTP, 1991) makes the determination of the LOAEL and NOAEL difficult. Histopathological changes were also observed in the kidneys of a different strain of rats (Wistar) at 2.5 mg/kg-bw/day and above (considered to be the LOAEL), but not at 1 mg/kg-bw/day (Harleman and Seinen, 1979).

Much is known about the metabolism of HCBD as it is directly related to its toxicity and carcinogenicity. Reactive metabolites, capable of binding with DNA and other cellular macromolecules and inducing mutations in Salmonella, are generated when the intermediate metabolite PCBC(1-(L-cysteine-S-yl)1,2,3,4,4-pentachlorobutadiene), arising from glutathione conjugation, is cleaved by renal beta-lyase.

The weight of evidence indicates that HCBD is genotoxic in the presence of appropriate metabolic activation systems. In bacterial assays in vitro, although results were negative both in the absence and presence of hepatic S-9 (Haworth et al., 1983; Reichert et al., 1983; Stott et al., 1981; De Meester et al., 1980), HCBD has induced gene mutation in the presence of GSH (Reichert et al., 1984), with a greater response where hepatic and renal microsomes were included (Vamvakas et al., 1988). HCBD has not been clastogenic in in vitro assays (Galloway et al., 1987; German, 1988). However, it induced chromosome aberrations in the bone marrow of mice administered HCBD by gavage (German, 1988) but not in rats exposed by inhalation (NIOSH, 1981) or in an early dietary investigation (Schwetz et al., 1977). Finally, it is noteworthy that a carcinogenic response only occurs in the presence of significant toxicity, suggesting that while a genotoxic mechanism cannot be ruled out, there are likely other factors contributing to the carcinogenic outcome.

In addition to seeking comments on the Tolerable Intake (TI), Health Canada also sought discussion on the following issues:

- The appropriate weight-of-evidence for genotoxicity.
- The possible mechanism(s) of action for the tumour induction.

Literature Search Discussion: Health Canada mentioned that an additional NTP study had been obtained since the file was sent for review. Reviewers agreed that there were no additional studies which should have been included, but suggested that in the future the literature search strategy be included in all files for peer review.

Hazard Identification for HCBD: Initial discussion centered on both the cancer and noncancer aspects of the assessment. Some reviewers felt that since the file only developed a noncancer value that the presenters had made an assumption that the cancers resulted from a threshold mechanism. Health Canada explained that under the Canadian Environmental Protection Act (CEPA), they were not required to do both a cancer and noncancer assessment; assessments focus on the most sensitive endpoint. In this case, the noncancer effects occurred at lower doses than that which induced tumours. Reviewers suggested presenting the Tumourigenic Dose 5% (TD05) for comparison.

In response to the question of evidence for a genotoxic mechanism, the reviewers felt that the data support a conclusion of genotoxicity but felt uncomfortable saying that genotoxicity was the critical step for tumour induction. Reviewers noted that the mitochondria appear to be the target for HCBD; more DNA adducts are found in the mitochondria than in the nucleus. The significance of mitochondrial DNA adducts is not clear. In addition, a great deal is known about the metabolism of HCBD. On the other hand, there are some negative genotoxicity studies, and the fact that HCBD induces only renal tumours at doses that are frankly toxic to the kidney support the possibility that these tumours are induced by nongenotoxic mechanisms. One reviewer noted that genotoxic chemicals do not cause cancer in tissues that are not actively dividing. Since the target for HCBD is the kidney, which is not actively dividing, then there must be another mechanism in addition to genotoxicity.

Health Canada did not present a cancer classification to the review group. However, the general agreement was that HCBD would probably fit into Group III -- possibly carcinogenic, under the current classification scheme for Priority Substances under CEPA..

Noncancer Critical Effect: There was consensus among reviewers that kidney lesions are the appropriate critical effect for HCBD. However, there was considerable discussion on whether the correct choice of NOAEL and LOAEL had been made. Specifically, in the NTP study (NTP, 1991) one female out of 10 at the lowest dose tested had kidney lesions. Since this incidence was not significantly different from controls, the dose had originally been judged as a LOEL (Lowest-Observed-Effect Level) and for the purposes of developing a TI considered as a NOAEL. However, one reviewer provided a personal communication from one of the authors of the NTP (1991) study which indicated that that the mouse in question had a higher severity score than what might have been expected. The authors had concluded that the effect seen in this mouse was due to HCBD treatment.

Reviewers agreed that choice of critical effect and effect level was supported by subchronic studies in rats (Schwetz et al., 1977) and mice (NTP, 1991). They also agreed to retain the designation of the lowest dose in the NTP study as a LOEL. In addition, the

peer review panel suggested that the sponsor consider obtaining information on the following items (if possible given constraints on resources, etc.) to determine if the finding in the low dose mouse was significant (that is, whether it should be considered as a LOAEL or as a NOAEL).

- check the historical controls for incidence and severity of this type of lesion
- check the rate of food consumption in the affected low dose mouse to be sure it had a comparable rate of consumption as other mice in the group
- ask NTP to reanalyze the kidney slides from the affected low dose mouse
- ask authors of the rat study for information on incidence/severity of nonneoplastic lesions

Uncertainty Factors: There was discussion regarding the relative sensitivity of rats and humans. One study (Lash et al, 1990) suggests that humans might be less sensitive than rats. However, one reviewer suggested that humans might be more sensitive than rats if conjugation with GSH is the key step in toxicity because humans have more GSH than rats. The general consensus of the panel was that too few data exist to modify the 10-fold default uncertainty factor for animal-to-human extrapolation; although, if supplemented, such data might be useful in this regard. There was also general consensus that an uncertainty factor of 10 was appropriate to account for sensitive subpopulations, since data were not available to indicate a different value. Whether an additional uncertainty factor was needed depended on answers to the issues identified above.

The peer review panel felt when these issues were addressed that if both the low doses in the rat and mouse study were consider LOAELs, then a 3-fold factor should be used for this area of uncertainty because of the steepness of the dose response curve and minimal nature of the toxic effect. If neither low dose was a LOAEL -- rather, both were NOAELs -- then no additional uncertainty factor was needed, and perhaps a lower overall factor than 100 would be appropriate. If only one of the low doses was a LOAEL, then Health Canada should make a judgment as to whether a 1-fold or 3-fold factor was needed in the determination of a TI, where steepness of the dose response slope might play some role in this determination.

Reviewers agreed that the database uncertainty factor of 5-fold was not needed since a Tumourigenic Dose is being calculated. Thus, the total uncertainty factor is either 100, or 300 for the stated reasons.

September 20, 1996

Participants:

Dr. John Christopher, California EPA
Dr. Michael Dourson, TERA, Chair
Dr. Marvin Friedman, Cytec Industries, Inc.

Dr. Michael Gargas, ChemRisk Division of McLaren/Hart
Dr. Patricia McGinnis, Syracuse Research Corporation
Ms. Bette Meek, Health Canada
Dr. Edward Ohanian, U.S. EPA
Dr. Jon Reid, University of Cincinnati

Presenter:

Dr. Susan Felter, TERA

Acrylonitrile (ACN) Presentation and Discussion

Marvin Friedman made a short presentation on the issues related to the ACN cancer assessment which his organization wanted discussed. Susan Felter made a short presentation on the draft assessment that had been distributed to reviewers prior to the meeting.

Acrylonitrile (ACN) is a monomer used extensively in the production of plastics, synthetic fibers, and rubbers. U.S. EPA previously categorized ACN in Group B1 (probable human carcinogen) and based an inhalation unit risk on an epidemiological study by OBerg (1980). However, subsequent epidemiological studies, including follow ups of the OBerg cohort, have not supported the conclusion that there is a causal relationship between ACN exposure and human cancer. In several strains of laboratory rats, ACN has been shown to be clearly carcinogenic by multiple routes of administration. ACN has been shown to be metabolized to 2-cyanoethylene oxide, a DNA-reactive epoxide. The genotoxicity results on ACN, however, are mixed, with a conspicuous lack of DNA adducts seen in vivo following administration of ACN. Based on new information primarily in the areas of epidemiological studies and mechanism of action, it appears that U.S. EPAs existing classification in Group B1 may no longer be supportable, and perhaps should be downgraded. Likewise, the basis for calculating an inhalation unit risk should be re-evaluated since the epidemiological data are not, taken as a whole, supportive of the 1980 conclusions of OBerg. Comment were solicited during the meeting on several topics key to the use of a rat inhalation bioassay by Quast et al. (1980). In an earlier evaluation of this study, U.S. EPA suggested combining tumor incidences from all sites in this study which were shown to have a statistically significantly increased tumor incidence (i.e., astrocytomas, Zymbal gland tumors, tumors of the small intestine and the tongue). Discussion points relevant to the hazard characterization and dose-response modeling for ACN are highlighted in the following bullets:

1. Can a quantitative cancer risk assessment be performed for an agent without reaching consensus on a formal classification under any given hazard characterization scheme?
2. What role do negative epidemiology data play in the risk assessment process? If a sensitivity analysis shows that the epidemiological data were sufficiently sensitive

to detect a cancer response, and they do not, should this be weighted more heavily than positive responses in animal bioassays?

3. How should tumors in animal bioassays be weighted if they are in organs of no, or questionable, relevance to humans? Examples that pertain specifically to ACN include tumors of the Zymbal gland.
4. How should inconsistent, or contradictory, genotoxicity data be used in a risk assessment? Should in vivo short term assays be given more weight than in vitro studies? Can positive findings in some studies be out-weighed by negative findings in other studies that are determined to be of greater relevance?
5. Can PBPK modeling be used even if the mechanism of toxicity is not fully understood? In the case of ACN, would it be appropriate to use a PBPK model based on the metabolism of ACN to cyanoethylene oxide?

Issue 1- Need for WOE classification: There was general agreement that the critical part of a weight-of-evidence analysis is a complete narrative description of the totality of the data available for a chemical. This description should draw conclusions about what the data say regarding the potential for the chemical to cause cancer in humans. However, there was not complete agreement on whether the weight-of-evidence narrative should place the chemical in a given "classification". Some reviewers suggested that classification schemes are strictly for regulatory purposes and that different schemes accomplish different purposes. By placing a chemical in a specific "box", a classification encourages people to think that the box establishes the risk, rather than the totality of the data. Thus, it is better to let readers draw their own conclusions from the data. However, other reviewers suggested that classifications are important to prevent readers from drawing conclusions that are unwarranted by the data. For example, without a statement of classification for ACN, readers might conclude that ACN is a known human carcinogen when that conclusion is not supported by the data. This problem could be overcome by including a discussion of how the chemical is classified by various agencies using different schemes.

Specific recommendation for ACN assessment: A narrative description without a classification is appropriate if the description includes classifications from various agencies (e.g., IARC and EPA assessments). The current description needs to strengthen the link between the data and the conclusions.

If inclusion of a "classification" is desired, it would be appropriate to use the EPA 1986 guidelines until the proposed 1996 guidelines are finalized. B2 seems an appropriate classification under the 1986 EPA guidelines.

Issue 2- How to use negative epidemiological data: Reviewers pointed out that for ACN the epidemiological data are not negative, just non-positive. If there were truly negative data, then the general agreement was that the human studies should be weighted more heavily than the animal studies. Reviewers suggested that a sensitivity analysis of human studies and a comparison of the dose-response relationships from both human and animal studies can help to answer these questions. An upcoming cohort study of 25,000 workers will provide useful data at an unspecified future date.

Specific recommendation for ACN assessment: The assessment should provide more complete information on the human studies in order to evaluate sensitivity. A sensitivity analysis should be conducted on the human studies and the data should be reviewed by an epidemiologist.

Issue 3- Use of tumors found in organs not relevant to humans: Reviewers concluded that an easy answer does not exist to this question and that case-by-case analysis is needed. When animals have tumors both in organs that are relevant and organs that are not relevant, combining these tumors for modeling will not have a significant difference on the result because models are generally more sensitive to dose than to response. Reviewers suggested that tumors should be combined only for a specific reason such as increase of statistical power or scientific relevance. Otherwise, it is more appropriate to use the most sensitive tumor type for modeling rather than combining. The more difficult question is what to model when there are only tumors in non-relevant organs, such as Zymbal gland or forestomach. In this case the overall weight of evidence and data on mechanisms of tumor formation are important considerations if the mechanism indicates that the chemical will act in the same manner on other organs, then the tumors should be modeled. However, if the tumors occur only at portal of entry and are due to tissue damage, they can more easily be judged as irrelevant.

Specific recommendations for ACN assessment: The assessment should model both CNS tumors alone and combined incidence of tumor types found individually to be statistically significantly reated to dose. A narrative to explain the differences in results should be included. Also, the assessment should show the proportion of benign to malignant tumors. Since there was high mortality, the assessment should include a mortality time-to-tumor analysis. Modeling of the CNS tumors should be the basis of the unit risk value.

Issue 4- Inconsistent genotoxicity data: There was a general consensus that in vivo genotoxicity data are more relevant than in vitro genotoxicity data. The significance of DNA adducts was discussed. One reviewer suggested that the presence or absence of DNA adducts is critical in assessing the genotoxicity of ACN. Specifically, the potential for genotoxicity is related to the metabolism of ACN to cyanoethylene oxide, which would be expected to form DNA adducts. The levels at which adducts are seen following administration of ACN, however, are exceedingly low.

Specific recommendations for ACN assessment: Reviewers agreed that the ACN data are suggestive of genotoxic mechanisms but that the evidence is somewhat difficult to decipher. Given that there are insufficient data to justify doing only a nonlinear dose-response assessment, a linear default should be used. The assessment should tabulate all genotoxicity data, with an emphasis on the in vivo data, to highlight the inconsistencies. If the overall evidence is mixed, a linear and nonlinear approach might be useful for quantification.

Issue 5- Use of PBPK modeling: There was general agreement that it is appropriate to use PBPK modeling for ACN with cyanoethylene oxide as the dose surrogate until additional data are available to determine more precisely the underlying mechanism. PBPK

modeling could be used to determine an internal dose at the brain which can then be used in the dose-response assessment modeling. This would be followed by back calculation to the rat external dose in order to extrapolate to humans. In addition, one reviewer suggested that it would also be appropriate to use the PBPK model on data from oral studies to extrapolate to an inhalation unit risk for comparison purposes.

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International Toxicity Estimates for Risk (*ITER*)
Peer Review Meeting -- September, 1996
Managing Potential Conflicts of Interest
(final with Panel concurrence)

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 has requested that each peer reviewer identify potential conflicts of interest related to the review of hexachlorobutadiene and acrylonitrile. Each reviewer has signed a statement indicating that they do not have a conflict of interest with these chemicals, with the following exceptions noted below. *TERA* has discussed these potential conflicts with the individuals and made recommendations. The panel reviewed these recommendations and reached the following conclusions.

John Christopher - Dr. Christopher is toxicologist with the California Environmental Protection Agency (Cal EPA). Cal EPA regulates various aspects of production, use, sale or disposal of many chemicals, including these two. However, Dr. Christopher does not have a specific conflict of interest and should participate fully in both discussions.

Michael Dourson - Dr. Dourson is the Director of *TERA* which developed the acrylonitrile assessment for CYTEC Industries. Because of the general nature of the acrylonitrile discussion, Dr. Dourson may participate fully and chair this part of the meeting.

Marvin Friedman - Dr. Friedman works for CYTEC Industries, the sponsor of the acrylonitrile assessment. Dr. Friedman may participate in the discussion of the acrylonitrile assessment, but not be polled for a recommendation.

Michael Gargas -- Dr. Gargas has published papers on acrylonitrile and remains active in research activities. However, Dr. Gargas is not an advocate of a particular position on this chemical. Dr. Gargas should participate fully in both discussions.

Patricia McGinnis - Dr. McGinnis works for Syracuse Research Corporation which has written documents on both of these chemicals for EPA prior to 1991. Dr. McGinnis has not worked on these projects and therefore there is no conflict of interest. Dr. McGinnis should participate fully in both discussions.

Bette Meek - Ms. Meek is the chief of the Priority Substances Section of Health Canada, the sponsoring organization for the hexachlorobutadiene assessment. Her organization is also developing a document on acrylonitrile. Ms. Meek should participate in both discussions, but not be polled for a recommendation on hexachlorobutadiene.

Edward Ohanian -- Dr. Ohanian works for the Office of Water of the U.S. EPA. The Office of Water (OW) is currently evaluating the oral toxicity of both of these chemicals and Dr. Ohanian has reviewed these documents; however, EPA has not taken firm positions on either assessment. Dr. Ohanian should participate fully.

Jon Reid -- Dr. Reid works for the University of Cincinnati and has not developed risk assessments, nor performed studies on these two chemicals. Dr. Reid should participate fully.