Appendix F

American Chemistry Council Ketones Panel Comments on the Draft IRIS Entry and Toxicological Review of Methyl Ethyl Ketone

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

American Chemistry Council *Good Chemistry Makes It Possible*

May 9, 2003

Susan H. Rieth
National Center for Environmental Assessment (8601D)
US Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Re: Draft Toxicological Review and Draft IRIS Summary for Methyl Ethyl Ketone (MEK)

Dear Ms. Rieth:

This letter and the attached comments are submitted on behalf of the American Chemistry Council Ketones Panel (Panel) to provide scientific comment on the above-referenced draft documents. The Ketones Panel includes the U.S. producers of MEK.[1]

The Panel appreciates EPA's efforts to update the IRIS database for MEK. The Panel believes the draft IRIS documents contain several improvements compared to the IRIS summary currently available online, which was last revised in 1993. MEK is an important commercial product, and an improved, up-to-date IRIS database accordingly is very important. The Panel urges EPA to complete the update process for MEK in a timely manner.

The Panel does have concerns, however, with the draft documentation. The Panel's first concern pertains to the IRIS update process; the Panel believes EPA's short time frame for public comment and decision not to provide public comments to the external peer reviewers undermines the purpose and effectiveness of the peer review. The Panel's substantive concerns pertain primarily to the Agency's interpretation of two key studies; NCEA has altered its interpretations of these studies (compared to the current IRIS database) without adequate explanation or justification. The Panel also has concerns pertaining to one aspect of NCEA's benchmark dose (BMD) methodology used to derive the inhalation reference concentration and oral reference dose. These concerns are presented in the attached comments.

---

[1] Members of the Panel are: Eastman Chemical Company, ExxonMobil Chemical Company, Celanese Ltd., Shell Chemical LP, and The Dow Chemical Company.

Any questions concerning these comments may be directed to William Gulledge, Manager of the Ketones Panel, at 703-741-5613, or william_gulledge@americanchemistry.com.

Sincerely,

Courtney M. Price/HCS

Courtney M. Price
Vice President, CHEMSTAR

Enclosure

cc: IRIS Submission Desk
c/o ASRC, Inc.
6301 Ivy Lane, Suite 301
Greenbelt, MD 20770

COMMENTS OF THE AMERICAN CHEMISTRY COUNCIL KETONES PANEL ON NCEA'S DRAFT TOXICOLOGICAL REVIEW AND DRAFT IRIS SUMMARY FOR METHYL ETHYL KETONE

May 9, 2003

The American Chemistry Council Ketones Panel (Panel) is pleased to provide scientific comment on the National Center for Environmental Assessment (NCEA)'s draft Toxicological Review and draft IRIS Summary for methyl ethyl ketone (MEK). The Ketones Panel includes the U.S. producers of MEK.[1]

The draft documents were posted on NCEA's web site on April 16, 2003 and apparently have been provided to external peer reviewers for their comment. NCEA states on its web site that while it was not soliciting public comments by the public posting of the documents, any scientific views received prior to May 9, 2003 would be considered in subsequent drafts.

The Panel appreciates NCEA's efforts to update the IRIS database for MEK. MEK is an important commercial product, and a current IRIS database accordingly is very important. The Panel first urged NCEA to update the IRIS database for MEK many years ago, and the Panel is anxious to see the update completed. Nothing in these comments is intended to delay that result.

The Panel believes the Draft IRIS Summary and Draft Toxicological Review of Methyl Ethyl Ketone contain a substantial amount of useful information. The derivation of the inhalation reference concentration (RfC) is substantially improved, compared to the current online IRIS database for MEK. NCEA has used total uncertainty factors for deriving both the oral reference dose (RfD) and RfC that are more scientifically appropriate than the current IRIS summary, yet both are still quite conservative. The Panel also agrees with NCEA's choice of the key study for derivation of both the RfD and RfC.

The Panel does have concerns, however, with the draft documentation. The Panel believes NCEA's short time frame for public comment, and its apparent decision not to provide public comments to the external peer reviewers, undermine the purpose and effectiveness of the peer review. The Panel's substantive concerns pertain primarily to the Agency's interpretation of two studies used to derive the RfD and RfC; NCEA has altered its interpretations of these studies (compared to the current IRIS database) without adequate explanation or justification. The Panel also has concerns pertaining to one aspect of NCEA's benchmark dose (BMD) methodology used to derive the RfD and RfC. These concerns and other technical comments are presented below.

---

[1] Members of the Panel are: Celanese Ltd., The Dow Chemical Company, Eastman Chemical Company, ExxonMobil Chemical Company, and Shell Chemical Company.

I. NCEA SHOULD PROVIDE GREATER OPPORTUNITY FOR PUBLIC COMMENT AND SHOULD PROVIDE COPIES OF PUBLIC COMMENTS TO THE EXTERNAL PEER REVIEWERS

The IRIS website posting for MEK provided interested parties with only 23 days to submit comments. Even for MEK producers, who are familiar with the database, 23 days is too short a comment period, given the volume of scientific literature available for MEK, the length of NCEA's draft documents, and the complexity of the BMD analyses presented in support of the RfC and RfC calculations. Moreover, NCEA has indicated on its web site that it is not actually soliciting public comments by the posting of the draft documents, though any scientific input that is received apparently will be considered in subsequent drafts. The Panel believes NCEA should encourage public comment, and provide a more reasonable time for preparation and submission of comments.

NCEA's IRIS documents are intended to serve as the starting point for all hazard and risk assessments conducted by EPA program offices. EPA also expects IRIS documents to be used by other federal and state agencies. Given the breadth and importance of NCEA's draft documents, the Panel believes NCEA should welcome scientific input from all quarters, and typically should provide at least 60 days for public comment.[2]

The Panel also believes NCEA should provide copies of any public comments to the external peer reviewers. If the peer review is to serve its intended purpose, the peer reviewers must have access to all relevant information, including scientific input and information provided by external parties, and especially including any scientific arguments or opinions that differ from those contained in the draft documents.

To command respect in regulatory and scientific communities, NCEA's IRIS files must be the product of an open and robust process, where public comment is encouraged and all comments are given fair consideration. The IRIS update process has been characterized as unduly protracted, but the process should not be rushed to conclusion by discouraging public comment and withholding public comment from the peer reviewers.

II. SUBSTANTIVE COMMENTS

1. Interpretation of Cox *et al*. (1975). The Panel agrees that this 2-generation rat reproductive effects study using 2-butanol (parent compound for MEK) provides no indication of reproductive toxicity at the highest dose level. The Panel also agrees that this study provides an adequate scientific basis for deriving an oral RfD. Considering the prior use of the study in IRIS to derive an RfD, the Panel sees no scientific reason not to continue to rely on the study. However, NCEA has modified its interpretation of the developmental effects reportedly seen in this study. Previously, NCEA considered 1771 mg/kg/day to be a NOAEL (see current on-line IRIS summary for MEK). NCEA now concludes that this dose is a LOAEL, based on reduced pup weight observed in the F1A litters but not F1B or F2 litters. The weight difference in F1A rats apparently is not statistically significant, but NCEA states that it considers the

---

[2] ATSDR typically provides more than 90 days for public comment on its draft toxicological profiles.

finding "biologically significant."[3] The Panel believes NCEA's original interpretation was correct, and that the new interpretation is not adequately explained or justified. The Panel notes that this study was recently reviewed by EPA scientists (and internationally) as part of approval of an OECD SIDS Dossier and SIAR for 2-butanol, and in that context 1771 mg/kg/day was regarded as a NOAEL.

2. BMD methodology for Derivation of Oral Reference Dose Based on Cox Study. NCEA has chosen a decrease of 5% in the mean pup or fetus body weight per litter (compared with the control mean) as the benchmark response "because it was a response rate that fell within the range of experimental dose levels."[4] The Panel does not believe EPA's statement is an adequate scientific justification for treating a 5% decrease in body weight as an adverse effect, particularly when 5% is less than one standard deviation, and the purported effect was not observed at 1771 mg/kg/day in the F1B and F2 litters. The Panel believes it would be scientifically more reasonable to use a 10% reduction in pup weight as the benchmark response, which would produce an ED_{10} of 1756 mg/kg/day and a LED_{10} of 1314 mg/kg/day.

More generally, NCEA has not presented complete information for how it selected the benchmark responses used throughout the draft IRIS documents for the BMD analyses. NCEA uses a 10% extra risk for misaligned sternebrae, and acknowledges that "the Benchmark Dose Technical Guidance Document recommends estimation of a 10% BMR for a point of consistent comparison across chemicals."[5] Yet elsewhere NCEA proposes to use a 5% change because "it was a response rate that fell within the range of experimental dose levels."[6] However, NCEA has not explained why that factor is relevant, or why it should not be considered a constraint on the BMD modeling outcome.

By adjusting the selection of the benchmark response, it is possible to affect the modeling result in ways that cannot be justified. By way of illustration, consider a situation where Chemical A has an observed response rate of 10% which is statistically significant, and Chemical B at the same dose has an observed response rate for the same effect of only 5% which is not statistically significant. By using a BMR of 10% in the first case and 5% in the second, one could make the two chemicals look similar for purposes of BMD modeling and subsequent derivation of an oral RfD. Yet the two substances obviously have different study results, and selection of a different BMR in each case would appear arbitrary.

3. Interpretation of Schwetz *et al*. (1991). NCEA has identified the LOAEL based on an increased incidence of misaligned sternebrae.[7] In the current online IRIS summary, the same concentration is identified as a LOAEL, but based on decreased fetal birth weight. The Panel agrees with the LOAEL/NOAEL designations, which are consistent in the current IRIS summary and the draft update documents, but does not believe the derivation of the RfC should

---

3 Draft IRIS Summary, p. 3.

4 *Id*.

5 *See*, e.g., Draft IRIS Summary, p. 13, citing U.S. EPA (2000).

6 See previous paragraph.

7 Draft IRIS Summary, p. 10.

be based on the purported incidence of misaligned sternebrae. The anomalous skeletal variation, misaligned sternebrae, was not common in the Cox et al, 1975 2-butanol study, Schwetz *et al*., 1974 MEK study, or Deacon et al, 1981 MEK study. While it may be considered "health protective" to use the finding that produces the lowest benchmark dose, it is too restrictive in this case to use the anomalous skeletal variation as the end point of choice because it was not a common finding: it was seen in only 1 of 4 studies. Also, the benchmark response was chosen as 10 % above the control mean. Since the control standard deviation is 10%, approximately 15% of the control litters have an "adverse finding." Fifteen percent is too large a portion of the controls to be adverse and is a further indication that the benchmark response is too restrictive.

NCEA's justification for selecting increased incidence of misaligned sternebrae as the basis for the RfC is that it is "the most health protective value." However, before modeling a toxicity endpoint, NCEA should make a scientific judgment concerning its biological significance, and NCEA ultimately should choose the most scientifically relevant toxicity endpoint for deriving an RfC or RfD. Further, NCEA's sound scientific judgment should not be set aside simply because one number is lower than another. In this case, the Panel believes decreased fetal birth weight is the more scientifically sound basis for identifying the LOAEL and NOAEL and for deriving an RfC.

4. Use of Duration Adjustment for Inhalation Developmental Toxicity Study. As stated in the introduction to these comments, the proposed RfC represents a substantial improvement, compared to the RfC in the current on-line IRIS summary for MEK. However, in deriving the RfC, NCEA has made a duration adjustment to the point of departure determined by BMD methodology.[8] However, the Panel has previously explained why it believes such a duration adjustment is not scientifically appropriate specifically in the case of MEK.[9] (This is an excellent example of the type of scientific information that the Panel believes should routinely be provided to external peer reviewers.) The Panel continues to believe NCEA has not presented an adequate scientific justification for applying a duration adjustment in this case. At the very least, NCEA should recognize that its approach adds an element of conservatism to the RfC calculation, such that the RfC value should be considered very health protective.

The Draft Toxicological Review acknowledges that "the available pharmacokinetic data indicate that MEK is rapidly absorbed, distributed, and metabolized, suggesting that duration adjustment may be inappropriate."[10] NCEA ultimately concluded there was not "sufficient evidence to argue convincingly for either peak exposure level or area under the curve," and so made "a health-protective duration adjustment," but the Panel respectfully disagrees for the reasons previously presented to NCEA.

5. Interpretation of Cavender *et al*. (1983). NCEA regards the high dose (5000 ppm) in this 90-day inhalation study in rats as a LOAEL, based on toxicity remote to the respiratory tract (reduced body weight gain, increased relative liver weight, and decreased brain

---

8 See Draft IRIS Summary, p. 10; Draft Toxicological Review of Methyl Ethyl Ketone, p. 67.

9 Keller and Pavkov, "A Duration Adjustment Is Not Appropriate for the MEK Developmental Toxicity Study," (February 2002) – previously submitted

10 Draft Toxicological Review, pp. 67-68.

weight).[11] This interpretation is consistent with the current IRIS database. However, the Panel has previously explained why it believes this high dose should be considered a NOAEL.[12] A change in liver weight, for example, unaccompanied by any evidence of pathology, should not be considered an adverse effect. The Panel notes that this study also was recently reviewed by EPA scientists (and internationally) as part of approval of an OECD SIDS Dossier and SIAR for 2-butanol, and the NOAEL of 5000 ppm was accepted.

The Draft Toxicological Review correctly notes:

> A subchronic inhalation study of MEK found no persistent body weight, gross behavioral changes, or histological changes in major tissues and organs in rats exposed 6 hours/day, 5 days/week for 90 days to concentrations as high as 5000 ppm (Cavender et al., 1983). Although some changes in organ weight and clinical pathology parameters were observed, these were not supported by histological changes.[13]

The Panel believes 5000 ppm should be regarded as a NOAEL.

6. Interpretation of Mitran *et al*. (1997). The Panel agrees with NCEA's reasons for not considering this study reliable. Weaknesses in the study have been recognized in previous reviews cited by NCEA, including one review conducted by EPA scientists. As a point of clarification, the Panel understands the California Office of Environmental Health Hazard Assessment (OEHHA) has withdrawn its draft Reference Exposure Level (REL) based on this study. This fact may be confirmed by contacting Dr. Melanie Marty of OEHHA. Accordingly, a correction should be made to the charge to the external peer reviewers, which indicates OEHHA is relying on this study.

CONCLUSION

The Panel appreciates this opportunity to provide comments on NCEA's draft documents for MEK, and hopes that the comments will be considered carefully. The Panel urges NCEA to complete the IRIS update process for MEK in a timely manner. More generally, the Panel urges NCEA in the future to allow a more reasonable comment period, and to provide copies of scientific comments to the external peer reviewers.

---

[11] Draft IRIS Summary, p. 16.

[12] J. Harkema, "Review of the Respiratory Histopathology Report from the 90-Day Inhalation Study of MEK by ToxicGenics," (Oct. 2001) – previously submitted

[13] Draft Toxicological Review, p. 45.