

Subsequently, EPA announced in the **Federal Register** (67 FR 1212, January 9, 2002) that it would undertake a formal IRIS review of MEK. The announcement recognized that in the decade since the initial IRIS assessment of MEK, substantive alterations in the Agency's methods for dose-response assessments have occurred. The estimated completion date for the assessment, including peer review and external peer review is September 2003. We will consider the results of that review prior to taking any final action related to the proposed rule.

In the meanwhile, to support statutory requirements and assist in the determination of the technical merits of the petition to delist MEK, EPA's ORD initiated a parallel undertaking to derive an interim health effects threshold for MEK inhalation exposure that incorporates consideration of current data and current EPA science policy. This process has resulted in the derivation of a prospective RfC of 9 mg/m³. The analysis underlying the development of this prospective RfC can be found in "A Prospective Reference Concentration for MEK (78-93-3)" which is in the docket for today's proposed action.

We consider this prospective RfC to be the most complete and current dose-response information on MEK and, therefore, have determined that it is the appropriate chronic noncancer health effects criterion for EPA to use in today's proposal to remove MEK from the HAP list. In our final evaluation about the potential for MEK to cause noncancer health effects, we will rely on the final RfC and other information resulting from the completed IRIS assessment. Thus, we will not take final action on today's proposed rule until such information becomes available. In today's action, we request comment generally on our prospective RfC and on the portion of our human health risk characterization based on this RfC. Also, because we recognize that there is some possibility that the RfC may change, we solicit comment on whether it would be appropriate for the Agency to delist MEK if the final RfC is different from the prospective RfC; for example, if it is finalized at 3 mg/m³, the level suggested by industry in its petition, or if it remains unchanged from the 1992 RfC of 1 mg/m³.

The prospective RfC is based on the same critical study as the 1992 IRIS. Consistent with recent Agency recommendations for developing RfD and RfC, the assessment incorporates a duration adjustment to the critical study's NOAEL. This approach adjusted the discontinuous inhalation exposure

(7 hours per day) in the critical study to a continuous (24 hours per day) duration. This procedure is premised on a simple concentration x time relationship, and it had the effect of reducing the adjusted NOAEL to 863 mg/m³ from the value of 2,978 mg/m³ used in developing the 1992 RfC.

Using the adjusted NOAEL, the assessment derives a human equivalent concentration (HEC) for MEK. The HEC represents an external air concentration estimated to achieve the same blood levels in humans and animals. Based on the available blood-to-air coefficient data for MEK in animals and humans, EPA applied the default factor of one for this derivation which resulted in a NOAEL_{HEC} of 863 mg/m³. As with the standard IRIS assessment, EPA applied uncertainty factors to the NOAEL_{HEC} to account for recognized areas of uncertainty in extrapolating the data to the appropriate human scenario. The EPA concluded that the 1992 IRIS interspecies uncertainty (UF=10) and the modifying factor (MF=3) should be revised. However, we concluded that the intraspecies uncertainty (UF=10) should remain unchanged.

The EPA applied the Agency's 1994 RfC methodology to the prospective RfC which results in an interspecies uncertainty factor of three. The prospective RfC also eliminates the previous modifying factor (MF=3) included in the 1992 IRIS to account for the absence of unequivocal data for portal-of-entry (respiratory tract) effects. This revision was, in part, due to additional information in a 1992 National Institute for Occupational Safety and Health (NIOSH) study in which 24 volunteers exposed to 590 mg/m³ of MEK for 4 hours reported no net complaints of even minor irritation. The consequence of that study was a decrease in the uncertainty around irritant type of portal-of-entry effects in humans.

The prospective RfC also addresses the 1992 IRIS database uncertainty factor (UF=10). The assessment states that the problematic situation that existed in 1992 persists; namely, the difficulty of establishing a health-based guideline for a lifetime chronic exposure without any toxicity studies involving lifetime chronic exposures. The existing long-term repeated exposure experiments have certain flaws that affect their use in developing an inhalation RfC. However, the assessment concludes that EPA can use information from existing studies, as well as ancillary information from new sources, to reduce the concerns in the database. The assessment concludes that the analysis, coupled with the totality of

the other available information, has the overall effect of reducing uncertainty in the database such that it is appropriate to apply a partial database uncertainty factor of three, rather than a full database uncertainty factor of ten, in developing the prospective RfC.

This reduction, taken with the reduction in interspecies UF and the elimination of the modifying factor, reduced the composite uncertainty from 3,000 to 100. Therefore, EPA concludes that the prospective RfC is 9 mg/m³.

D. Human Health Risk Characterization and Conclusions

Methyl ethyl ketone is currently listed in IRIS based on a 1989 evaluation as "not classifiable as to human carcinogenicity" according to the 1986 Cancer Guidelines. The IRIS summary identified the lack of both animal and human data to assess the carcinogenic potential of MEK, and at the current time, animal cancer bioassays with MEK by either the oral or inhalation route are still lacking, and there are no indications that such studies are either ongoing or planned. However, genotoxicity information does not indicate any readily apparent genetic mechanism of action for MEK, and the existing genotoxicity tests for MEK are essentially negative. In addition, structural data on MEK do not support any readily apparent basis for a carcinogenic hazard.

The retrospective cohort studies of worker populations exposed to MEK provide no clear evidence of a cancer hazard in these populations. Because of various study limitations, these studies are weak and cannot support conclusions about the carcinogenic potential of MEK in humans. A case-control study examining the association between paternal exposures to several solvents including MEK and childhood leukemia is exploratory in scope such that we cannot use the results to reliably support the existence of any such association. Overall, this epidemiologic evidence is inconclusive and weak from which to draw conclusions about carcinogenic risks in the human population, although there is some suggestion between increased risk for some cancers and multiple solvent exposures, which included MEK. However, we consider the inconclusive nature of these studies to be offset by more conclusive results regarding the low potential of MEK to be carcinogenic, including the overall lack of positive results from genotoxicity tests and mutagenicity tests, and the lack of any indication of carcinogenicity from structure-activity relationships. Consequently, we conclude that we may