

some indication that MEK is not likely to be a reproductive toxicant.

The IRIS assessment of MEK states that at present, there is no convincing experimental evidence that MEK is neurotoxic “\* \* \* other than possibly inducing CNS (central nervous system) depression at high exposure levels.” The IRIS documentation shows that no peripheral neurohistopathological changes were reported in rats exposed continuously to 3,320 mg/m<sup>3</sup> MEK for up to 5 months (Saida *et al.*, 1976). No treatment-related central or peripheral neurohistopathology was observed in rats exposed for 90 days (6 hours/day, 5 days/week) at concentrations of MEK as high as 14,865 mg/m<sup>3</sup>, even among animals specifically prepared and examined for neurohistopathology (Cavender *et al.*, 1983). Also, ten of ten rats exposed to MEK at 17,700 mg/m<sup>3</sup> and higher for 8 hours/day, 7 days/week, died in the 7th week of exposure without neurological symptoms or histopathology (Altenkirch *et al.*, 1978).

Methyl ethyl ketone has been shown to potentiate neurotoxicity of other solvents in experiments with laboratory animals when both MEK and the other solvent are present in high concentrations. The EPA addressed the issue of interactions such as this in the text of the prospective RfC. We described several studies with human volunteers (*see* Dick *et al.*, 1992, and references therein) that have MEK exposure groups (at 100 parts per million (ppm) coexposed to relatively low levels, also around 100 ppm) of several other solvents including acetone, methyl isobutyl ketone and toluene. At least for the brief exposure periods in those studies (around 4 hrs), the authors observed no evidence of neurotoxic interactions. However, a recent review (Noraberg and Arlien-Soborg, 2000) reports evidence of possible interactions even at occupational concentrations below the threshold limit values (TLV) (200 ppm, 590 mg/m<sup>3</sup>) in solvent mixtures containing MEK at 200–300 ppm and n-hexane at 60 ppm. This point should be considered when evaluating mixtures of solvents, especially those containing MEK and the solvents listed above, especially n-hexane. However, the lower limits of MEK exposure that may result in potentiation with other solvents have not been well established, and the potential of MEK in this regard remains a concern, although a minor one. Such concerns are especially diminished at the low-levels we are concerned with in this assessment (*i.e.*, much less than 590 mg/m<sup>3</sup>).

The petition presents a short-term criterion of 33 mg/m<sup>3</sup>, which is an

adjustment of their RfC of 3.3 mg/m<sup>3</sup>. The petitioner calculated this value by simply eliminating the uncertainty factor of ten that is used for extrapolating from subchronic to chronic exposure in the RfC. We do not agree that this is an appropriate method of arriving at an short-term human health effects criterion, however, currently there is no EPA human health criterion for short-term exposures available for us to use in an analysis.

There are 1999 California Environmental Protection Agency (CalEPA) short-term health criteria (CalEPA 1999). The CalEPA published three levels of acute reference exposure levels (REL) to protect against mild adverse effects (associated with a 1-hour exposure), severe effects (associated with a 7-hour exposure), and life threatening effects (associated with a 1-hour exposure). The REL for mild effects is 13 mg/m<sup>3</sup>, for severe effects it is 32 mg/m<sup>3</sup>, and for life threatening effects it is 1,385 mg/m<sup>3</sup>. For the purposes of our analysis and decision, we focused on the mild REL, to be health protective. The CalEPA acute REL to protect against mild effects is based on the study of Nakaaki (1974). However, we consider the results with MEK from the studies of Dick *et al.* (1984, 1988, 1989, 1992) to be more scientifically defensible for the purposes of our analysis. Compared to the Nakaaki study, the Dick *et al.* studies tested more subjects (20+ per study versus four), used control groups extensively, better controlled the exposures (constant in the Dick *et al.* studies versus increasing concentrations in Nakaaki), analyzed a greater number of endpoints, and apparently longer duration exposures. Collectively, the volunteer studies of Dick *et al.* indicate that exposures to MEK of up to 200 ppm (590 mg/m<sup>3</sup>) and up to 4 hours would be an acceptable nonadverse effect concentration in the general population for both subjective effects (such as objectionable odor or irritancy) and for neurobehavioral effects. We would expect the same nonadverse effect concentrations to be relevant for children, as there is no reason to consider children as a sensitive subgroup for such a highly subjective, nonadverse effect as mild irritancy.

#### *C. Determination of an Appropriate Health Effects Criterion for Chronic Noncancer Effects*

For risk assessments which estimate chronic noncancer effects from inhalation exposures, the IRIS inhalation RfC is the primary quantitative consensus value used by the Agency.

The RfC for MEK of 1 mg/m<sup>3</sup> was placed on IRIS in 1992. It was derived from the Schwetz *et al.* (1991) developmental toxicology study by dividing the NOAEL (2,978 mg/m<sup>3</sup>) by a series of uncertainty factors (UF). The UF for the determination of the MEK RfC was 3,000. This overall uncertainty factor reflects uncertainties in interspecies extrapolation (UF=10), sensitive individuals (UF=10), and an incomplete database, including a lack of chronic and reproductive toxicity studies (UF=10). In addition, a modifying factor (MF=3) was used to account for the absence of unequivocal data for portal-of-entry effects. This resulted in a combined UF and MF of 3,000.

It is Agency policy that the IRIS represents a starting point for risk assessments, however, it is not given conclusive weight in the context of rulemaking. If an outside party questions information presented in the IRIS, we will consider all credible and relevant information before us in the course of making our decision.

Accordingly, the petitioner reviewed the IRIS RfC in light of guidelines published by EPA in 1994, which addressed and updated methods for calculating RfC. Applying these guidelines to the same critical IRIS developmental study used to derive the IRIS RfC, which used the older methodology, the petitioner proposed a revised health criterion based on a reduction of the MEK uncertainty factor for interspecies extrapolation. This involved a reduction of the interspecies UF of 10 to a default value of 3. The reduction in the interspecies UF is consistent with the guidelines and is warranted if standard default dosimetric adjustments are incorporated in the original study. As a result, the petitioner proposed a revised RfC value of 3.3 mg/m<sup>3</sup> (which we view as being equivalent to 3 mg/m<sup>3</sup> since EPA generally expresses the RfC as a whole number).

The EPA's Office of Research and Development (ORD) reviewed the petitioner's proposed revision to determine whether such an alternative RfC was appropriate. That review indicated that the method that the petitioner applied to derive the criterion was consistent with both EPA policy and guidance. However, ordinarily, it is Agency policy that revisions in the IRIS are performed such that the entire database is simultaneously reevaluated for all effects and for all routes of exposure. This is done for both administrative efficiency and to ensure that we evaluate the breadth of available science.