

maximum individual exposures would be up to a factor of ten less than the maximum exposures presented in the petition. Therefore, in light of our review of the petitioner's exposure analysis, we have concluded that exposures to annual average ambient concentrations of MEK may not reasonably be anticipated to exceed 1 mg/m<sup>3</sup>, and that the maximum 24-hour exposures may not reasonably be anticipated to exceed 10 mg/m<sup>3</sup>. Also, based on our own analysis, we have concluded that maximum 1-hour exposures may not reasonably be anticipated to exceed 25 mg/m<sup>3</sup>.

#### B. Human Health Effects Assessment

We determined that the petition uses the same toxicological database as the 1992 IRIS assessment of MEK to characterize human health effects and to identify an appropriate human health criterion for the risk characterization for chronic effects. The IRIS is the Agency's official repository of consensus human health risk information. It was created and is maintained by the Agency to provide assistance to Agency decision makers on the potential adverse human health effects of particular substances. In addition, we evaluated recent studies reported in the published literature.

Methyl ethyl ketone is classified in the IRIS (1992) as a Group D compound. A Group D compound is one that is not classifiable as to human carcinogenicity. This classification is based on the absence of human carcinogenicity data and inadequate animal data. There are no animal cancer bioassays of MEK by either the oral or inhalation route. There are structural data on MEK. One study concludes that MEK is unlikely to be carcinogenic based on the lack of any structural features or alerts indicative of carcinogenic potential as a result of mechanism-based structure-activity relationship (SAR) analysis (Woo *et al.*, 2002). Further, Woo has given MEK a low concern rating (unlikely to be of cancer concern) based on comparison to acetone for which there is no evidence of carcinogenicity, and the fact that there is no evidence that unsubstituted mono-ketones have been associated with carcinogenicity/genotoxicity. There is also no reason to anticipate any electrophilic reactivity for unsubstituted mono-ketones mentioned above (*i.e.*, no structural alerts).

Cancer data on humans from which to draw conclusions about potential carcinogenic risks to the human population are weak and limited. None of the occupational epidemiology studies we examined (four studies of three different worker cohorts were available) provided clear evidence of

increased cancer risk from occupational exposure to MEK. These data do provide some suggestion of evidence of an increased risk between multiple solvent exposures which included MEK and some cancers including bone and prostate cancer. (Alderson and Rattan, 1980; Wen *et al.*, 1985; Spirtas *et al.*, 1991; Blair *et al.* 1998.)

One study that has received some attention is a 1987 study investigating potential carcinogenic effects in the children of males occupationally exposed to MEK (Lowengart *et al.*, 1987). This study included 123 matched pairs of children whose fathers reported, by questionnaire only, occupational exposure to various compounds including MEK, chlorinated solvents, spray paints, dyes and pigments, and cutting oils. The study reported a statistically significant positive trend for risk of childhood leukemia based on father's frequency of use for all of the chemicals mentioned, including MEK. Paternal exposure to MEK also appeared elevated, but not statistically significantly so, for the period of paternal exposure after birth of the child but not during pregnancy or one year before pregnancy. This study is considered as an exploratory study, based solely on questionnaires with no other exposure information. Factors that could be confounding covariates such as exposures to other chemicals and personal lifestyle were not taken into account in the statistical analysis of this study.

Methyl ethyl ketone has been tested for activity in an extensive spectrum of *in vitro* and *in vivo* genotoxicity assays and has shown no evidence of genotoxicity in most conventional assays (National Toxicology Program, no date; World Health Organization 1992; Zeiger *et al.*, 1992). Methyl ethyl ketone tested negative in bacterial assays (both the *S. typhimurium* (Ames) assay, with and without metabolic activation, and *E. coli*), the unscheduled deoxyribonucleic acid (DNA) synthesis assay, the assay for sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells, the mouse lymphoma assay, the assay for chromosome aberrations in CHO cells, and the micronucleus assay in the mouse and hamster. The only evidence of mutagenicity was mitotic chromosome loss at high concentrations in a study of aneuploidy in yeast *S. cerevisiae*; the relevance of this finding to humans is questionable. Overall, studies of MEK yield little or no evidence of genotoxicity.

Overall, the epidemiologic evidence is weak from which to draw conclusions about the carcinogenic risk in the human population. While none of the

studies provides clear evidence of an increased cancer risk, with the totality of the evidence considered inconclusive, the data do provide some suggestion of an increased risk between multiple solvent exposures which include MEK and cancer, specifically childhood leukemia, bone cancer and prostate cancer. There is, however, an absence of positive results in the majority of mutagenicity and genotoxicity tests which are designed to indicate the potential for carcinogenicity, and there is a lack of structural features or alerts indicative of carcinogenic potential in SAR analysis. Based on these results we believe that MEK may not reasonably be anticipated to be carcinogenic.

Developmental toxicity was the basis for the IRIS RfC of 1 mg/m<sup>3</sup> which was verified in 1992. The critical study in the derivation of the RfC involved Swiss mice that were exposed to 0; 1,174; 2,978; or 8,906 mg/m<sup>3</sup> MEK for 7 hours per day during gestation days 6 through 15 (Schwetz *et al.*, 1991). Neither material nor developmental toxicity was observed at the low- or mid-doses. At the highest dose, there was a decrease in fetal body weight that was significant only in males. There was also a significant trend in the incidence of misaligned sternebrae when measured on a fetus but not a litter basis. At the highest dose, there was also an increase in relative liver and kidney weight, but the toxicological significance of that effect, if any, is reported in the IRIS as unknown. The lowest observed adverse effect level (LOAEL) for this study was 8,906 mg/m<sup>3</sup>, and the no observed adverse effect level (NOAEL) was 2,978 mg/m<sup>3</sup>.

The available data indicate that MEK is not likely to be a reproductive toxicant. There exists no inhalation reproductive toxicity study of MEK; however, an oral two-generation reproductive/developmental toxicity study of 2-butanol, a metabolic precursor to MEK, is available and is the basis for the oral reference dose (RfD) for MEK (Cox *et al.*, 1975). 2-Butanol is quantitatively converted to MEK within the body. In this two-generation study, administration of 2-butanol to rats in drinking water at concentrations as high as 3 percent (~5000 mg kilograms-day) did not affect reproductive performance, but did induce developmental effects consistent with the results from inhalation developmental toxicity studies in rodents. The absence of any pathological lesions in the reproductive organs of rats exposed to MEK by inhalation for 90 days to concentrations as high as 14,865 mg/m<sup>3</sup> also provides