MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 19, 1996

TO: File for Methylethylketoxime (96-29-7)

FROM: Marco Bianchi

SUBJECT: Initial Risk Screening Level

The initial risk screening level (IRSL) for methylethylketoxime is 2.5 ug/m^3 based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide, ACGIH Guide, TSCA 8(e) Triage Database, and American Industrial Hygiene Association Workplace Environmental Exposure Level Guide .

Allied Signal has published both oral and inhalation acute toxicity data for Sprague-Dawley rats. The LD_{50} was determined to be between 2.3-3.7 g/kg, while the LC_{50} was listed at >1350 ppm.

In a subacute inhalation study by Dow Corning, groups of 10 male and 10 female rats were exposed to concentrations of 0, 60, 283, 533, or 714 ppm, 6 hrs/day, 5 days/week, for 4 weeks. The most significant findings included mild increases in blood mean corpuscular volume, mean corpuscular hemoglobin, reticulocyte count, and red blood cell count at 533 and 714 ppm. Spleen weights were increased in these groups, and hemosiderosis in the spleen was seen at 714 ppm. Consistent with the studies with oral and subcutaneous administration, the hemosiderosis may have been the result of red blood cell hemolysis. Exposures of 60 and 283 ppm were no-observed-effect-levels.

An autoradiography study to evaluate metabolism and pharmacokinetics was conducted using ^{14}C-labeled MEKO. In this study, mice were given single oral (300 mg/kg) or intratracheal (10 mg/animal) doses of MEKO and serially were sacrificed up to 24 hr. post-dosing. MEKO was absorbed rapidly from the stomach and lungs, and the ^{14}C-label was found in all tissues with a high degree of metabolic activity. It was assumed that MEKO was rapidly hydrolyzed to methyl ethyl ketone which then entered the 2-carbon pool (tricarboxylic acid cycle).

MEKO was negative in an Ames Assay, both with and without metabolic activation. In addition, it was negative in an *in vitro* sister chromatid exchange (SCE) assay using concentrations as high as 1%. In a mouse lymphoma assay, MEKO was reported as the cause of an increase in mutation frequencies of 2.4- to 5.4-fold in cultures treated with 2.8 to 6.5 ug/ml of MEKO. None of the S-9 treated cultures exhibited significant increases in mutant frequency when compared to controls, however. According to the authors, this may indicate a tendency for mammalian organisms to detoxify MEKO.

There was no data from the studies mentioned above that gave any indication that MEKO was carcinogenic. Upon review of the TSCA 8(e) Triage Database, an abstract was found that described this compound as being oncogenic. A request was made to Allied Signal, the company that submitted the abstract, for carcinogenicty data to conduct a risk assessment on this compound.

Allied Signal forwarded a two specie bioassay; an inhalation oncogenicity study of methylethylketoxime in rats and mice. In this study, methylethylketoxime was administered by whole body inhalation as a vapor to Fischer 344 rats (80/sex/group) and CD-1 mice (60/sex/group). The test substance was administered for 6 hours per day, 5 days per week, for approximately 18 months at 0, 15, 75, and 375 ppm to mice, and the same administration regimen and doses for rats, except for the study duration which lasted approximately 26 months. Particle size distribution determinations indicated no significant test substance aerosol was present in the exposure chambers for either study.

In the mouse study, detailed physical examinations were conducted on all animals pretest and weekly thereafter. Following approximately 12 months of exposure, up to 10 animals/sex/group were sacrificed, selected organs were weighed and organ/body and organ/brain weight ratios calculated. At termination of the study, the control group survivorship was 43% in the males and 61% in the females. There was no difference in survivorship among any of the exposure groups including controls. The physical observations, opthalmoscopic and body weight results indicated no signs of any MEKO-related effects. Microscopically, findings which appeared to be related to treatment included changes in the nasal turbinates and in the liver. In the turbinates, degenerative and reparative changes were observed. These included desquamation of olfactory epithelium, dilation of submucosal glands with debris and inflammatory cells in the glands and in the nasal lumen and with proliferation of squamous or respiratory epithelium. In some areas the hypertrophic cells from the glands appeared to be extending to the luminal surface and replacing the lost epithelium. The liver changes indicating hepatoxicity, included pigment in reticuloendothelial cells, necrosis, centrilobular hepatocellular hypertrophy and granulomatous inflammation. There was also an increase in liver carcinomas in the 374 ppm male group relative to control and the other exposure groups.

In the rat study, detailed physical examinations were conducted on all animals pretest and weekly thereafter. Following approximately 3, 12, and 18, months of exposure, up to 10 animals /sex/group were sacrificed, selected organs were weighed and organ /body and organ/brain weight ratios calculated. At termination of the study, in the control group survivorship was 34 % in the males and 60% in the females. There was no difference in survivorship among any of the exposure groups including controls. The physical observations and body weight results indicated no signs of any MEKO-related effects, except for opacities. Opthalmoscopic examinations of the animals found a dose related increase in cataracts and a treatment-exaggerated incidence of corneal dystrophy. The dystrophic changes seen in the 374 ppm group were far more severe than in other groups. This increase was probably the result of MEKO exaggerating a strain-related condition already present. There were a number of treatment-related microscopic findings. Congestion of the spleen with pigment in reticuloendothelial cells and extramedullary hematopoiesis appeared to be treatment related in the 374 ppm animals at the 3-, 12-, and 18 month sacrifices. However, at the terminal sacrifice these findings were masked by high incidences of mononuclear cell leukemia in animals other than the 374 ppm animals and could not be evaluated. Findings which appeared treatment related at 12 and 18 months and in the chronic study were seen in the liver and nasal turbinates. The liver changes were increased incidence of basophilic foci and hepatocellular vacuoles and decreased incidence of hyperplasia/proliferation of the biliary duct and perbiliary fibrosis. The liver changes were increased incidence of hepatocellualr carcinoma and adenoma and spongiosis hepatis. In conclusion, under the exposure conditions of this study, MEKO was a liver oncogen in the male rat at 75 ppm.

The IRSL was derived by AQD staff using the above study, based on carcinogenic effects using the methodology from Rule 231. The highest q_1^* value was produced by the data from hepatocellular adenomas in rats. Doses were adjusted from parts per million to mg/m^3 doses, and the number of animals per group were adjusted to include only those mice surviving until the time of the first tumor appearance. The Global82 model was used for this quantitative risk assessment.

Sex/Species	Tumor Type	q_1^* (ug/m3)$^{-1}$
Male rat	hepatocellular adenoma	4.0 E-4

MLE dose on 1 x 10-6 risk = 3.5343684561 E-03
95% Upper Confidence Interval = 1.399909 E-06

$$q_1^* = \frac{1.399909\ E-06}{3.5343684561\ E-3} = \ 4.0\ E-4$$

Milligram to microgram conversion:

4.0 E-4 (mg/m^3) x 1E-3 = 4.0 E-7 ug/m^3

IRSL and SRSL determination:

$$IRSL = \frac{1E-6}{4.0\ E-7} = 2.5\ ug/m^3$$

$$SRSL = \frac{1E-5}{4.0\ E-7} = 25\ ug/m^3$$

IRSL = 2.5 $\mu g/m^3$ based on annual averaging
SRSL = 25 $\mu g/m^3$ based on annual averaging

MB : ma