# Developmental Toxicity of Inhaled Methyl Ethyl Ketone in Swiss Mice

B. A. SCHWETZ,[1] T. J. MAST,* R. J. WEIGEL,* J. A. DILL,* AND R. E. MORRISSEY[2]

*Developmental and Reproductive Toxicology Group, Division of Toxicology Research and Testing, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709; and *Battelle Pacific Northwest Laboratory, P.O. Box 999, Richland, Washington 99352*

Developmental Toxicity of Inhaled Methyl Ethyl Ketone in Swiss Mice. SCHWETZ, B. A., MAST, T. J., WEIGEL, R. J., DILL, J. A., AND MORRISSEY, R. E. (1991). *Fundam. Appl. Toxicol.* **16**, 742–748. Methyl ethyl ketone (MEK) is a widely used industrial solvent to which there is considerable human exposure. To assess the potential for MEK to cause developmental toxicity in rodents, groups of Swiss (CD-1) mice were exposed to 0, 400, 1000, or 3000 ppm MEK vapors 7 hr/day on Days 6–15 of gestation. Groups consisted of about 30 bred females each. Exposure of pregnant mice to these concentrations of MEK did not result in overt maternal toxicity although there was a slight, treatment-related increase in relative liver weight which was statistically significant in the 3000 ppm group. Mild developmental toxicity was observed in the 3000 ppm group in the form of a reduction in mean fetal body weight. This reduction was statistically significant for the males only, although the relative decrease from the control values was the same for both sexes. There was no increase in the incidence of resorptions or the number of litters with resorptions among mice exposed to MEK. There was no significant increase in the incidence of any single malformation, but several malformations which were not observed in the concurrent control group or the controls of contemporary studies were present at a low incidence—cleft palate, fused ribs, missing vertebrae, and syndactyly. There was also a significant trend for increased incidence of misaligned sternebrae, a developmental variation. In summary, pregnant Swiss (CD-1) mice were relatively insensitive to the toxic effects of MEK at the inhaled concentrations used in this study. However, the offspring of the mice exhibited significant signs of developmental toxicity at the 3000 ppm exposure level. Neither maternal nor developmental toxicity was observed at 1000 ppm MEK or below. © 1991 Society of Toxicology.

Methyl ethyl ketone (MEK) is a widely used industrial solvent with a 1984 production figure of 556,000,000 lbs. (Yang, 1986, and references therein). Inhalation of MEK vapors and skin contact with liquid MEK are the major routes of human industrial exposure. The ACGIH (1988) has adopted a TLV of 200 ppm and a short-term exposure limit of 300 ppm for MEK.

The toxicology literature on MEK has been thoroughly reviewed by Yang (1986). Animal studies have shown MEK to cause relatively little toxicity from acute or short-term repeated exposures. For example, a 90-day inhalation study of MEK in male and female F344 rats exposed to 0, 1250, 2500, or 5000 ppm MEK 6 hr/day 5 days/week produced no adverse effects on the clinical health or growth of either sex (Cavender *et al.*, 1983). While this study showed no evidence of neurotoxicity, MEK is known to potentiate *n*-hexane-induced neu-

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rotoxicity as well as that caused by other hydrocarbons (Altenkirch et al., 1978). MEK also potentiates the hepatotoxicity of chloroform. MEK has not been found to be mutagenic in mammalian or bacterial cell systems, but causes aneuploidy in yeast (Yang, 1986, and references therein).

The metabolism of MEK has been well characterized and is similar for all species examined—guinea pigs (Di Vincenzo et al., 1976), rats (Dietz and Traiger, 1979), rabbits (Sanoyeshi, 1911), and humans (Perbellini et al., 1984). The elimination half-life from serum was found to be 270 min following ip injection in guinea pigs (Di Vincenzo et al., 1976). MEK is well absorbed through the skin; Munies and Wurster (1965) reported the presence of MEK in expired air within 2–3 min following application of the solvent to the skin of humans. The rate of elimination from the blood is independent of the route or mode of exposure. Induction of the cytochrome P450 systems by MEK and/or its metabolites has been demonstrated by Abdel-Rahman et al. (1976). Toftgard et al. (1981) also found increased liver weights and cytochrome P450 content of the liver of rats exposed to 800 ppm MEK for 6 hours/day 5 days/week for 4 weeks.

Developmental toxicity studies with MEK have been reported in rats. Schwetz et al. (1974) exposed timed-pregnant Sprague–Dawley rats to concentrations of 0, 1000, or 3000 ppm MEK on Days 6–15 of gestation. MEK exposure had no effect on resorptions, fetal crown–rump length, sex ratio, or on the maternal body weight or weight gain during gestation. Fetal body weight was slightly decreased for both exposure groups but the decrease was statistically significant only at the 1000 ppm level. Major malformations were observed only at 3000 ppm—one fetus in each of four litters. Two of these fetuses were acaudate and two were brachygnathic. There was a significant increase in the percentage of litters having fetuses with reduced ossification of bones and extra ribs at both concentrations of MEK. The incidence of soft tissue anomalies (subcutaneous edema and dilated ureters) was also greater in the MEK-exposed groups than the controls and this increase was statistically significant in the 3000 ppm group.

As a result of the findings of Schwetz et al. (1974), another study was conducted by Deacon et al. (1981), also in Sprague–Dawley rats. In this study, sperm-positive rats were exposed to 400, 1000, or 3000 ppm MEK, 7 hr/day on Days 6–15 of gestation. The dams did not exhibit any clinical signs of toxicity but decreased weight gain and increased water consumption were observed at 3000 ppm. As in the earlier study, there was no significant effect on the mean number of live fetuses or resorptions per dam. The percentage of litters with fetuses exhibiting delayed ossification of vertebral centra was increased in the highest exposure group, as in the earlier study. Also as previously reported, the percentage of litters with fetuses having reduced ossification of skull bones was lower in the 3000 ppm exposure group than in any of the other groups. While the reduction in the incidence of reduced ossification of the skull bones is of uncertain importance, both studies supported a conclusion that developmental toxicity was observed—in the presence of maternal toxicity in one study and in its absence in the other.

Epidemiologic studies have also supported that exposure may be associated with adverse effects on human development. Holmberg and Nurminen (1980) reported a statistically significant increase in the incidence of children born with central nervous system defects following maternal exposure to organic solvents during the first trimester of pregnancy when compared to children of unexposed mothers. MEK was among the organic solvents to which the affected cohort was exposed. These authors further reported that no significant difference in the incidence of children with such defects was found when occupational exposures to metals, pesticides, dyes, noise, temperature extremes, fumes, or radiation were used as the analysis variable. Thus, because of the large number of people exposed to MEK and because the results of two studies in rats suggested that MEK may be a developmental toxicant,

this study was conducted to evaluate the developmental toxicity of inhaled MEK in a second species of laboratory animal, Swiss (CD-1) mice. The concentrations of MEK selected for this study were chosen to duplicate those used in a previous developmental toxicity study in rats (Deacon et al., 1981) and because 3000 ppm was anticipated to be an appropriately high concentration for a study in mice.

## MATERIALS AND METHODS[3]

*Animals and animal husbandry.* Four groups of female Swiss mice [(COBS) (Crl:CD-1)(ICR)BR Swiss Albino mice][4] 12 weeks of age at the beginning of the studies, were exposed to either filtered air as the control group or 400, 1000, or 3000 ppm MEK vapors, 7 hr/day for 10 consecutive days. Each of the four exposure groups consisted of 10 virgin and 33 plug-positive female mice. All groups were randomly selected using body weight as a blocking variable. Virgin mice were included to assess maternal toxic effects which may result solely from the state of pregnancy. The day of plug detection in mice was designated as Gestation Day 0. Pregnant mice were killed on Gestation Day 18 and virgin females were killed 3 days after the last exposure. Control animals were housed in an exposure chamber in the same room and were handled in the same manner as the mice that were exposed to MEK. Mice were housed in quarantine rooms for 4 weeks prior to start of exposures. Males and females were housed separately on stainless-steel wire racks equipped with automatic waterers. During the quarantine period, six males and four females were killed and examined for gross and microscopic lesions. Nasal pharyngeal washes from these animals were cultured for bacterial pathogens and serum from each animal was tested for antibodies to selected pathogens. Another check for antibodies was performed on serum obtained at the final euthanization from five females in the control and highest exposure groups. All results were negative for significant pathogens and lesions. Study animals were observed daily for mortality, morbidity, and overt signs of toxicity.

Food[5] was provided free-choice during the entire time the animals were in the test facility except during the 7-hr daily exposure when it was removed to prevent contamination. Room lighting was maintained on a 12-hr

cycle (0600–1800 for the light phase). Mean chamber temperatures during the study were maintained within the limits of $75 \pm 3°F$. Mean percentage relative humidity in all exposure chambers was within the specified limits of $55 \pm 15\%$.

*Test chemical and exposures.* MEK (CAS No. 78-93-3) used for this study had an initial percentage purity greater than 99.9%, confirmed by infrared spectrometry. For inhalation exposures, 2.3 $m^3$ stainless-steel chambers were used which contained three levels of caging, each of which was split into two offset tiers.[6] Filtered air containing a uniform mixture of MEK flowed through the chamber at approximately 15 $ft^3$ per min to provide 15 air changes per hour. Within the chambers, air flow, vacuum, temperature, relative humidity, and test chemical concentrations were monitored at approximately 4-hr intervals. MEK vapor was generated by a rotary evaporation system which produced high purity MEK vapor. Nitrogen was introduced at low pressure to force MEK vapors out of the evaporator flask. The mixture of nitrogen and MEK were thoroughly blended with a conditioned air stream prior to entry into the chamber. Uniform distribution of the vapors in the chamber was confirmed. The concentrations of MEK in the chambers were monitored with a gas chromatographic system having an estimated precision of $\pm 1\%$ and detection limit of 0.5 ppm. MEK was not found in the control chamber air or in the air surrounding the chambers in the exposure room.

*Observations.* Female mice were weighed at intervals of 3–5 days throughout the study. On Gestation Day 18, bred mice were killed with $CO_2$, weighed, and examined grossly for signs of maternal toxicity. Maternal liver and kidney weights were recorded. Apparently nongravid uteri from mated females were stained with 10% ammonium sulfide to detect possible implantation sites. The number, position, and status of implants were recorded for each gravid uterus. Placentas were examined and discarded. Live fetuses were weighed and examined for gross defects, and their sex was determined by internal examination of the gonads after a lethal injection of Nembutal. Fifty percent of the live fetuses and any fetuses with gross external abnormalities were examined for visceral defects by dissection of fresh tissues. The heads of 50% of the live fetuses were removed and placed in Bouin's fixative. After fixation the heads were serial-sectioned with a razor blade and examined for soft tissue craniofacial abnormalities. All fetal carcasses were prepared for skeletal staining. Cartilage as well as ossified bone was visualized by double-staining with alcian blue and alizarin red S. The individual identity of each skeletal and head specimen was maintained throughout the study.

*Statistical analyses.* All means and standard deviations for animal data were analyzed using the SAS general linear models procedure (SAS, 1985) with an analysis of variance model for unbalanced data. Response variables, either body

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[3] The NTP report of this study will be available through the National Technical Information Service. This study was conducted in accordance with FDA's Good Laboratory Practice, Regulations for Nonclinical Laboratory Studies (FDA, 1978).

[4] Charles River Breeding Laboratories, Raleigh, NC.

[5] NIH-07 diet, Ziegler Brothers, Inc., Gardner, PA.

[6] Harford System; Lab Products, Inc., Aberdeen, MD.

TABLE 1

SUMMARY OF THE METHYL ETHYL KETONE EXPOSURE
CHAMBER CONCENTRATIONS (ppm) DURING A
DEVELOPMENTAL TOXICITY STUDY WTIH MICE

| | Exposure group (ppm) | | |
|---|---|---|---|
| | 400 | 1000 | 3000 |
| Mean ± SD | 398 ± 9 | 1010 ± 28 | 3020 ± 79 |
| Maximum | 439 | 1140 | 3340 |
| Minimum | 352 | 894 | 2490 |
| % Samples | | | |
| ± 10% of target | 100 | 98 | 99 |

weight or the arcsin transformations of proportional in-
cidence data, were analyzed against the class variable
"treatment" in a one-way analysis of variance model. A
Tukey's $t$ test (two-tailed) was used to assess statistically
significant differences between control and exposed groups.
If appropriate, the dose–response relationship was deter-
mined by means of an orthogonal trend test (Winer, 1971).
In the case of proportional data, the $t$ tests and trend anal-
yses were performed on transformed variables. The litter
was used as the basis for analysis of fetal variables.

## RESULTS

The average concentrations of MEK in the
chambers during this study are summarized

in Table 1. The average purity of MEK in un-
occupied chambers and the distribution line
to the chambers was 99.4% during test gen-
eration and 99.9% in chambers occupied by
animals during the exposures. Thus, the tech-
niques used to generate MEK vapor for the
inhalation exposures did not affect its stability.

There were no differences in MEK toxicity
between the virgin and pregnant female mice
(data not shown). Therefore, the adult toxicity
data referred to in the rest of this report is for
the pregnant females. The mean pregnancy
rate of the bred females was 82% with no sig-
nificant difference in pregnancy rates between
the MEK-exposed and the control groups.
Mean body weights and weight gains were not
affected by exposure to MEK at any time dur-
ing the study when compared to the 0 ppm
group (Table 2). The relative liver weight of
the 3000 ppm group was significantly higher
than the corresponding control relative liver
weight. The relative kidney weight for the 3000
ppm group was also significantly greater than
the control value; however, since the mean
relative kidney weight was essentially the same
for the 400 and the 3000 ppm groups, and
lower for the 1000 ppm group, this change
was probably not biologically important.

TABLE 2

METHYL ETHYL KETONE MOUSE DEVELOPMENTAL TOXICITY STUDY: MEAN BODY
AND ORGAN WEIGHTS, AND EXTRAGESTATIONAL WEIGHT GAINS

| | | Exposure group (ppm) | | | |
|---|---|---|---|---|---|
| | | 0 | 400 | 1000 | 3000 |
| Body wt | n = | 26 | 23 | 26 | 28 |
| GD 6 | | 28.8 ± 1.7[a] | 28.4 ± 1.9 | 28.8 ± 1.8 | 28.7 ± 1.9 |
| GD 9 | | 31.5 ± 1.8 | 31.2 ± 2.1 | 31.4 ± 2.1 | 31.8 ± 2.0 |
| GD 15 | | 44.7 ± 3.4 | 44.2 ± 3.6 | 44.0 ± 3.3 | 45.0 ± 3.8 |
| GD 18 | | 53.3 ± 5.1 | 52.2 ± 5.1 | 51.9 ± 4.1 | 53.0 ± 4.9 |
| Extragestational wt gain[b] | | 6.9 ± 1.4 | 6.5 ± 1.6 | 6.5 ± 1.9 | 7.6 ± 2.0 |
| Uterine wt | | 20.1 ± 3.6 | 19.3 ± 3.7 | 18.8 ± 2.9 | 19.1 ± 2.7 |
| Relative organ wt (g/100 g body wt) | | | | | |
| liver | | 5.28 ± 0.61 | 5.16 ± 0.62 | 5.41 ± 0.36 | 5.67 ± 0.41* |
| kidney | | 0.82 ± 0.07 | 0.87 ± 0.11 | 0.85 ± 0.05 | 0.87 ± 0.07* |

[a] Grams, mean ± SD.
[b] Maternal weight gain during gestation corrected for gravid uterine weight.
* Significantly different from control, $p < 0.05$.

Exposure of pregnant mice to MEK vapors on Gestation Days 6–15 did not affect the number of implantations or the percentage of live fetuses or intrauterine deaths per litter as compared to the controls (Table 3). Reductions in body weight of both male and female fetuses were significantly correlated with increasing concentrations of MEK, with the difference from control being statistically significant at 3000 ppm for males but not at lower concentrations. However, both males and females body weights were lower than the control group by the same relative amount, about 4%. The number of live fetuses per litter that were malformed and the number of litters with one or more malformed fetuses was increased in the MEK-groups compared to the controls but the differences were not statistically significant on the basis of either the number of fetuses or litters affected or the mean number of malformed fetuses affected per litter. However, there were four malformations (Table 4) observed in exposed groups that were not present in either the current control or in contemporary control groups. These malformations consisted of three fetuses with cleft palate (two in the 400 ppm group and one in the 1000 ppm group), two with fused ribs (one in the 1000 ppm group and one in the 3000 ppm

group), one with missing vertebrae in the 1000 ppm group, and five with syndactyly all from a single litter in the 3000 ppm group. Although there was not a significant trend for an increase of malformations with respect to increasing concentration of MEK, the 3000 ppm group did have a higher combined incidence of malformations than did either of the two lower exposure groups.

Gestational exposure to MEK resulted in a significant, treatment-related increase in the incidence of misaligned sternebrae with respect to the control group (Table 4). The increase (not statistically significant) in the mean percentage per litter of total variations was due mostly to the increase in misaligned sternebrae.

## DISCUSSION

Exposure of pregnant Swiss (CD-1) mice to 0, 400, 1000, or 3000 ppm MEK did not result in apparent maternal toxicity, although an exposure-related increase in the relative liver-to-body-weight ratio was present and statistically significant at 3000 ppm MEK. This increase in liver weight, above the increase normally observed during pregnancy, may be related to

TABLE 3

METHYL ETHYL KETONE MOUSE DEVELOPMENTAL TOXICITY STUDY: *IN UTERO* DEVELOPMENT

| | Exposure group (ppm) | | | |
|---|---|---|---|---|
| | 0 | 400 | 1000 | 3000 |
| Implantations/dam | $12.4 \pm 2.3^a$ | $12.2 \pm 2.2$ | $12.3 \pm 1.8$ | $12.3 \pm 1.8$ |
| Live fetuses/litter | $11.9 \pm 2.3$ | $11.3 \pm 2.5$ | $11.2 \pm 1.6$ | $11.5 \pm 1.9$ |
| Resorptions/litter | $0.5 \pm 0.8$ | $0.9 \pm 1.0$ | $1.1 \pm 1.1$ | $0.7 \pm 0.8$ |
| Dead fetuses/litter | 0 | $0.0 \pm 0.2$ | 0 | $0.1 \pm 0.3$ |
| Litters with resorptions | 9/26 | 12/23 | 16/26 | 16/28 |
| Fetal wt, male (g) | $1.38 \pm 0.07$ | $1.38 \pm 0.06$ | $1.34 \pm 0.10$ | $1.31 \pm 0.08^*$ |
| Fetal wt, female (g) | $1.32 \pm 0.08$ | $1.33 \pm 0.08$ | $1.31 \pm 0.06$ | $1.27 \pm 0.08$ |
| % males | $50 \pm 12$ | $47 \pm 13$ | $43 \pm 15$ | $51 \pm 18$ |
| No. live fetuses malformed/litter (%) | 1 (0.3) | 3 (1.2) | 3 (1.0) | 9 (2.8) |
| No. litters with malformed fetuses (%) | 1 (3.8) | 3 (13.0) | 3 (11.5) | 5 (17.9) |

$^a$ Mean ± SD.
* Significantly different from control, $p < 0.05$.

TABLE 4

METHYL ETHYL KETONE MOUSE DEVELOPMENTAL TOXICITY STUDY: MALFORMATIONS AND VARIATIONS

| | Exposure group (ppm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 400 | 1000 | 3000 | 0 | 400 | 1000 | 3000 |
| | No. fetuses[a] | | | | No. litters | | | |
| Malformations | 310 | 260 | 291 | 323 | 26 | 23 | 26 | 28 |
| Cleft palate | 0 | 2 | 1 | 0 | 0 | 2 | 1 | 0 |
| Fused ribs | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| Limb flexure | 1 | 1 | 0 | 3 | 1 | 1 | 0 | 3 |
| Missing vertebrae | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Syndactyly | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 1 |
| Variations | | | | | | | | |
| Sternebrae | | | | | | | | |
| misaligned | 31[b] | 27 | 49 | 58 | 18 | 14 | 18 | 21 |
| fused | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| reduced ossification | 6 | 6 | 16 | 14 | 5 | 4 | 11 | 7 |
| Supernumerary ribs | 56 | 44 | 58 | 65 | 17 | 13 | 15 | 22 |
| Skull-reduced ossification | 3 | 3 | 2 | 5 | 2 | 2 | 2 | 2 |

[a] All fetuses were examined for external and skeletal defects; one-half had head removed prior to skeletal staining for soft-tissue craniofacial evaluation. Visceral examinations were performed on approximately 50% of live fetuses and all fetuses with external defects.

[b] Significant trend, $p < 0.05$.

enzyme induction as reported for rats by Toftgard et al. (1981). Developmental toxicity was observed in the present study in the form of a significant decrease in fetal body weight at 3000 ppm MEK as well as a significant trend for an increase in the incidence of misaligned sternebrae, a skeletal variation. The incidence of fetal malformations in the MEK-exposed groups, although not statistically significantly different from control, is of some concern since several malformations were present which were not observed in concurrent or contemporary control groups of the same strain of mouse. The percentage of litters having fetuses with malformations was also greater for all MEK exposure groups than for the controls, although the differences were not statistically significant.

The results of this study in mice are reminiscent of those reported previously in two studies in Sprague–Dawley rats (Schwetz et al., 1974; Deacon et al., 1981) where major malformations were found in only the 3000 ppm

group. The relative sensitivity of rats and mice for an effect on fetal body weight is unclear since in the present study fetal body weight was significantly reduced at 3000 ppm but not at lower concentrations; fetal rat weights were significantly reduced at the 1000 ppm level but not at 3000 ppm (Schwetz et al., 1974). Considering these three studies collectively, MEK caused developmental toxicity in the presence of mild maternal toxicity in rats and mice, and, in one rat study, in the absence of maternal toxicity.

The developmental toxicity of 2-butanol, a known metabolite of MEK, was investigated by Brightwell et al. (1987) in Sprague–Dawley rats. Pregnant females were exposed by inhalation to 3500, 5000, or 7000 ppm 2-butanol, 7 hr/day, throughout gestation until they were killed on Day 20. Maternal toxicity was evident at the highest concentration, as manifested by a reduction of weight and food consumption. There was no increase in the incidence of fetal malformations at any

concentration of 2-butanol. A reduction in mean fetal body weight was observed at the 7000 ppm concentration. Thus, at least one metabolite of MEK was not developmentally toxic even when administered at concentrations above those used for the parent compound in this study.

In summary, the results of this developmental toxicity study of inhaled methyl ethyl ketone in mice are similar to those reported earlier for rats; in both species, developmental toxicity has been observed in the presence of mild maternal toxicity, and a low incidence of malformations along with other evidence of developmental toxicity. In the present study in mice, no maternal or developmental toxicity was observed at concentrations of 1000 ppm MEK or below.

## ACKNOWLEDGMENTS

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